WORKERS' COMPENSATION - APPEALS
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AN ANALYSIS OF HEALTH EFFECTS OF ARSENIC AND ITS INORGANIC COMPOUNDS AND RECOMMENDATIONS FOR AN OCCUPATIONAL STANDARD

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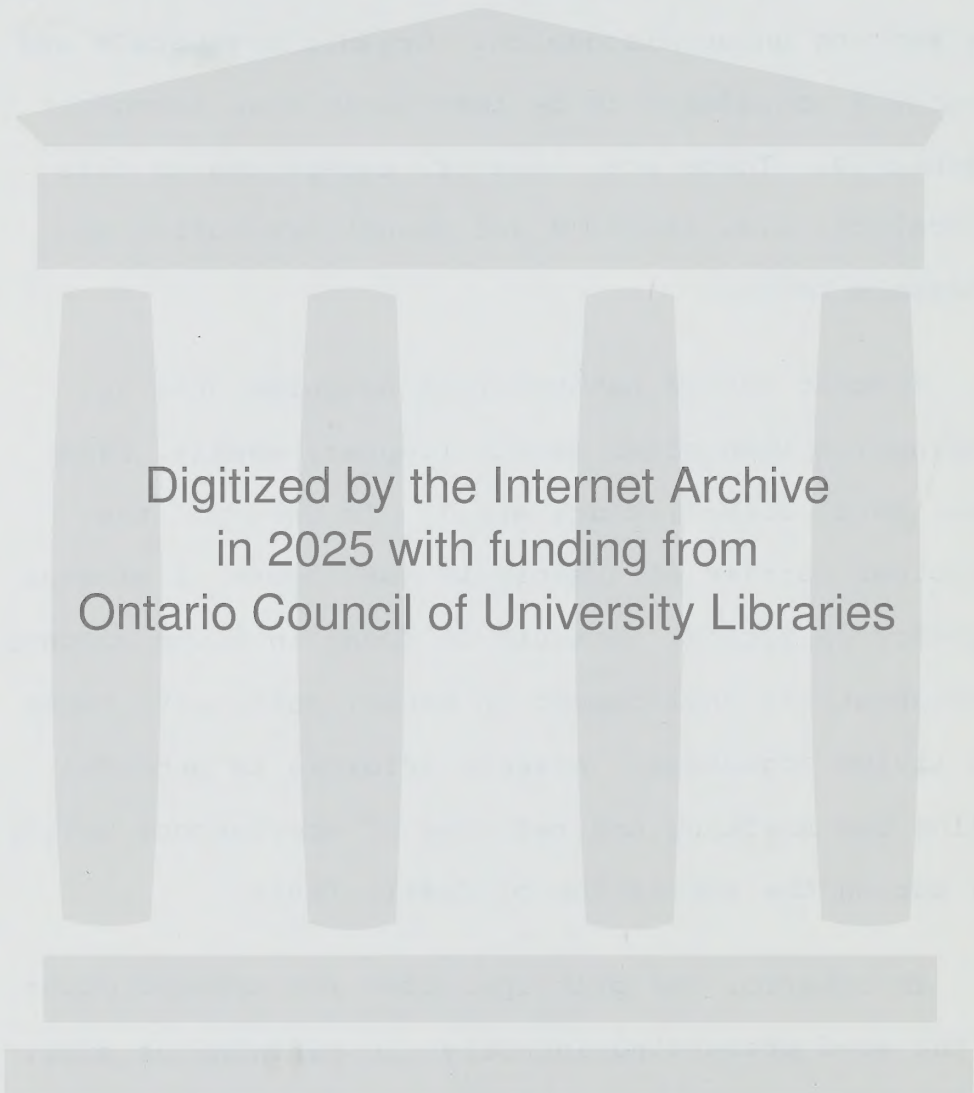
ARSENIC AND ITS INORGANIC COMPOUNDS

This document is a review of the health effects of arsenic and its inorganic compounds. Reference to organic arsenic compounds will be made in this document when it is believed that such references will clarify the subject under discussion. Organic arsenicals are generally considered to be less toxic than inorganic arsenicals. There are, however, exceptions to this generality, i.e. lewisite and phenyl arsenoxide are extremely toxic.

Arsenic occurs naturally in sulphide ores in combination with other metals (copper, cobalt, iron, lead, gold, silver, zinc, etc.). In Ontario, the principal carrier of arsenic in most types of mineral deposits is pyrite. Arsenic is found in trace amounts throughout the environment in water, soil, air, rocks and living organisms. Arsenic trioxide is produced during the smelting and refining of non-ferrous metals and during the combustion of fossil fuels.

In Ontario, the principal uses for arsenic occur in the wood preserving industry, in refining of zinc, in some pharmaceuticals, and as arsine in the semi-conductor industry. In other jurisdictions, arsenic is also used in the production of insecticides and pesticides.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Natural sources of atmospheric arsenic include volcanic action, hot springs, decay of plant matter and other microbial actions and the weathering of minerals within soils.

Physical and Chemical Properties

Arsenic (As) is an element occurring in Group V of the periodic table. Its physical and chemical properties closely resemble those of phosphorus. The atomic number is 33, atomic weight 74.9. Arsenic exhibits three valence states: -3, +3, +5.

Arsenic compounds may be classified into two groups: (1) inorganic arsenic compounds, (2) organic arsenic compounds.

Arsine is considered to be the most toxic form of arsenic. The toxicity of the other arsenicals from most to least toxic is believed to be as follows - inorganic trivalent > organic trivalent > inorganic pentavalent > organic pentavalent > elemental arsenic, (NRC, 1978). In addition to the variation due to chemical form arsenic varies in toxicity among species.

This report will be concerned primarily with inorganic arsenic compounds. Most compounds of arsenic when heated in the presence of air are converted to arsenic trioxide. Because arsenic trioxide sublimes at

193°C, it is easily carried in suspension on other small particles in the air. For this reason, emissions of arsenic from processes in which heat is involved are generally in the form of arsenic trioxide. Most of the available data on toxicity to humans relates to exposure to inorganic trivalent arsenic compounds.

METABOLISM

Absorption

Arsenic may enter the body through inhalation, ingestion or percutaneous absorption.

Absorption by Inhalation

The absorption of inhaled arsenic compounds is dependent upon chemical form, and, to a great extent, particle size. Large particles are trapped by the mucous membranes of the nose and throat, swallowed and then enter the gastro-intestinal tract to be either absorbed or excreted. The smallest particles remain in suspension in the inhaled air, and are exhaled. The particles which are in the range between these two extremes - approximately 0.1 to 1.0 micron are the optimal size for deposition in the respiratory tract.

It is believed that a very substantial portion of the arsenic which is inhaled is absorbed through the lung and enters the general circulation.

Studies by Holland et al. (1959) on human inhalation of cigarette smoke containing 250 μg ^{74}As showed that 4.8 - 8.8% of the total arsenic present in the aerosol was deposited in the respiratory tract. On the other hand, a much greater portion, i.e. 32-62%, was deposited following inhalation of a solution nebulized to produce an aerosol of similar arsenic concentration.

They then noted that after the inhalation of either arsenic-containing cigarette smoke or an equally concentrated arsenic aerosol, 75-85% of the arsenic deposited in the lung tissue was absorbed into the blood within 4 days. After 14 days, cumulative arsenic absorption increased to 85-90% of the total deposited. The pattern of arsenic distribution in the respiratory tissues and the absorption rates from these tissues into the bloodstream were similar despite differences in the aerosol characteristics of the two exposure conditions.

Uptake by Ingestion

Absorption of arsenic from the digestive tract is dependent upon the chemical form of the compound, purity of the compound, valence and particle size.

There are a number of published estimates of average daily intake of arsenic from food in non-

occupationally exposed persons. The average Canadian consumes approximately 0.03 mg As daily (Smith et al. 1973). In comparison, an average daily American diet[a] contains 0.9 mg As/day ; a Japanese diet, 0.07-0.17 mg/day, (Underwood 1971) and an English diet, 0.09 mg/day, (WHO 1973). Frost (1967) observed that 3 mg As_2O_3 (2.3 mg As) per day produced no overt signs of acute toxicity in humans. Sandi in the Report of the Task Force on Arsenic in Ambient Air, (Health and Welfare Canada, 1975) estimated the average intake of Arsenic from Canadian diets to be less than 100 µg per day. This area is controversial and exact rates of absorption of dietary arsenic from the digestive tract cannot as yet be calculated. Absorption of arsenic from particulate matter greater than one micron in diameter from the stomach has been estimated to be approximately 5-15%, (NRC 1978).

Distribution

Following absorption, inorganic arsenic is found initially in the circulatory system, a small amount (approximately 4%) is bound to the globulin of hemoglobin in the red blood cells and the remainder is contained in the blood plasma, (Axelson, 1980).

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[a] The data for American diets were taken from the work of Schroeder and Balassa (1966) and are probably too high.

In most species except the rat arsenic leaves the blood within 24 hours and is distributed to body tissues. Most of the arsenic is associated with the protein fraction of the tissues, with a small amount in the acid soluble fraction and only a trace in the lipoid fraction. (Peoples, 1964). After absorption arsenic levels are higher in liver, kidney, lung, spleen, bone, muscle and skin, smaller amounts are found in brain, heart and uterus, (Buchanan, 1962; Oehme, 1972). Bone, muscle and skin represent the major storage areas of arsenic in the body due to their mass. In normal subjects 25% of the administered arsenic was retained after 48 hours whereas only 10% remained after 10 days. (NRC 1978).

Arsenic does not readily cross the blood-brain barrier in humans, however, neurological manifestations of arsenic poisoning indicate that it is not without effect on the brain. This may be due to the binding of arsenic with sulphydryl groups in enzyme systems. In humans transplacental transfer of arsenic occurs. (Vallee et al, 1960). The whole body, biological half-life of arsenic has been estimated to be in the range of 125-250 days (Bowen, 1975). The biological half-life of organically combined arsenic is much shorter, in the range of 2-3 days. Fish and crustaceans are the usual source of organic-arsenicals in the human diet.

Elimination

Arsenic is excreted predominantly in the urine, to a lesser extent in sweat and feces, and minimally through ectodermal tissue - mainly hair and nails. Excretion takes place rapidly. In an experiment using human volunteers, Holland et al. (1959) demonstrated that approximately 28 per cent was excreted within the first 48 hours after ingestion and 45% had been excreted within 10 days. An additional 2.5 per cent had been excreted in the feces after 10 days, but the remaining 52.5 per cent was not accounted for.

Normal values for non-occupationally exposed persons are given in Table I. (U.S., DHEW, 1976).

There is some evidence of the oxidation of trivalent arsenic to the pentavalent state in humans. The first day after an injection of inorganic arsenic in humans, Mealey (1959) discovered that of the excreted inorganic arsenic, 28% was As(III) and 63% was As(V) in urine samples. After 7 days, the urine contained inorganic arsenic in the ratio 15% As(III) to 78% As(V). Schroeder and Balassa (1966) suggested that as a general rule, As(V) is excreted in the urine whereas As(III) is excreted primarily via bile and intestines.

Crecelius (1976) compared human excretion

following ingestion of arsenic-contaminated wine, well water and canned crabmeat. Normal urinary levels approximated 1.5 ppb As(III), 1.5 ppb As(V), 3 ppb MAA (methyl arsonic acid - $CH_3AsO(OH)_2$), and 8 ppb DMAA (dimethyl arsinic acid - $(CH_3)_2As(OH)$. Within 5-10 hours after ingestion of 450 ml wine containing 50 µg As(III) and 13 µg As(V), the urinary levels of the above chemical species increased five-fold. This suggested the in vivo formation of methylated arsenic compounds. Inorganic arsenic levels in the urine returned to normal 20 hours following ingestion, whereas organic arsenic levels reached a maximum at 40 hours, decreasing to normal 85 hours after ingestion. Of the total arsenic ingested 63 µg, 80% was excreted within 61 hours; 50% of this was DMAA, 14% was MAA while As(III) and As(V) accounted for 8%.

The relationship of occupational exposure to airborne arsenic, body burden, the effect on health and levels of arsenic in blood, urine, feces, hair and nails are all of interest. Arsenic in urine is considered to be the most reliable indicator of recent exposure. For groups of workers a fair correlation exists between arsenic in air levels and arsenic in urine. A relationship between airborne arsenic and total urinary arsenic in individual workers was demonstrated by Pinto, Varner et al. (1976) and the relationship is roughly linear. The conversion factor

postulated in this paper (urinary arsenic in µg/litre x 0.31 = airborne arsenic in $\mu g/m^3$) has been used in many papers and discussions. More recent work by Carlsson (1976) and Buchet, et al. (1981) have produced very similar conversion factors if you consider the variations in protocol used in these studies.

Urine arsenic levels in individual exposed workers are not generally considered to be an accurate reflection of airborne arsenic exposure, although group urine As levels are well correlated with group airborne As exposure.

On this basis it would seem that arsenic in urine should be measured in workers as an indication of their exposure at work and elsewhere and utilized to detect excessive exposure and direct the attention of workers, industry and their attending physicians to areas and sources of excessive exposure and methods of reducing it.

Toxicity

The toxicity of arsenic compounds varies with valence, and chemical composition. Inorganic arsenic compounds are considered to be more toxic than organic arsenic compounds, however, there are exceptions to this generality, (i.e. lewisite and phenylarsenoxide are extremely toxic). Some of the early data on

toxicity of arsenic compounds varies as the compounds used were more or less pure. Trivalent compounds are in general more toxic than pentavalent forms.

Trivalent inorganic arsenic compounds when absorbed into the body inhibit the activity of many enzymes which contain sulphydryl groups. It is believed that the trivalent inorganic arsenic binds to the sulphydryl groups of lipoic acid, thereby inhibiting the pyruvate dehydrogenase system. By blocking pyruvate oxidation, arsenic interferes with cellular respiration, the main energy producing process in aerobic cells. In addition to pyruvate dehydrogenase other enzyme systems inhibited by trivalent arsenic include acetylcholinesterase, desoxyribonuclease, d-amino acid oxidase, 2-glutamic acid oxidase, monoamine oxidase, transaminase, liver choline oxidase, choline dehydrogenase, glucose oxidase, etc., (Buchanan, 1962). It is to this interference with a wide spectrum of enzyme systems that the effects of arsenic on many organ systems are attributed.

Arsenic toxicity has been studied extensively in various species of animals and in man. Experiments have demonstrated a marked species difference in the resistance to acute poisoning with arsenic trioxide. The lethal oral dose for most species appears to be between 1 and 25 mg/kg of body weight when administered

as sodium arsenite and three to ten times that figure as arsenic trioxide (National Academy of Sciences, 1977). The LD_{50} of a pure aqueous solution of arsenic trioxide for Swiss-Webster mice was reported to be 39.4 mg/kg body weight and for Sprague-Dawley Albino rats 15.1 mg/kg of body weight (Harrison et al. 1958).

The fatal oral dose of arsenic trioxide for man is reported to be between 70 and 180 mg (1-2.5 mg/kg body weight) if there is no clinical treatment (Vallee et al. 1960).

Health Effects

(a) Acute Arsenic Poisoning

Acute arsenic poisoning is almost always the result of ingestion of inorganic arsenicals. Symptoms may occur as soon as 30 minutes after ingestion or may be delayed for several hours if the arsenical was ingested with food.

Cases of poisoning are characterized by profound gastro-intestinal damage producing nausea, vomiting, abdominal pain and diarrhea which may result in shock and subsequent oliguria, albuminuria and death. The most sensitive organs in acute arsenic poisoning are the liver and kidney. Other reported acute symptoms are facial oedema, muscular cramps and cardiac abnormalities. Acute intoxication with arsenic

compounds is usually followed by anemia and leukopenia, particularly granulocytopenia.

Exposure to some arsenic compounds in air such as arsenic trioxide can cause acute damage to the mucous membranes of the respiratory system, exposed skin and the conjunctiva. Perforation of the nasal septum has been observed in some individuals after only a few weeks of exposure to arsenicals.

Recovery from acute poisoning may be followed in 1-4 weeks by exfoliative dermatitis and peripheral neuropathy. About five weeks after exposure, white transverse lines (Mee's Lines) may be seen in the fingernails and toenails.

(b) Acute Arsine Poisoning

Inhalation of arsine causes rapid intravascular hemolysis. Symptoms of headache, dyspnea, nausea and vomiting have been observed 2 to 24 hours after exposure. In severe cases abdominal pain, haematuria and jaundice appear rapidly (Nielson, 1968). Death is caused by acute renal failure, apparently the result of massive tubular damage due to intratubular precipitation of haemoglobin. (Fowler, 1974). The extreme acute toxicity of arsine is well known; 250 ppm for 30 minutes may be fatal, and 3-10 ppm can cause symptoms of poisoning in a few hours. (ACGIH--TLV

documentation 1980).

(c) Chronic Arsenic Poisoning

As a result of exposure to arsenicals over a long period of time, irritation of the mucous membranes of the respiratory tract and the skin have been noted frequently. There have been a number of reports of involvement of the nervous and circulatory systems and the liver.

Irritation of the mucous membranes results in conjunctivitis, rhinitis, laryngitis and/or bronchitis and in some cases perforation of the nasal septum.

Arsenical skin lesions vary somewhat depending on the type of exposure. Eczematoid symptoms of varying degrees of severity occur. In occupational exposure to airborne arsenic skin lesions may result from local irritation. Two types of dermatological disorders may occur:

1. an eczematous type with erythema, swelling and papules or vesicles;
2. a follicular type with erythema and follicular swelling or follicular pustules.

Dermatitis is primarily localised on the most heavily exposed areas such as the face, back of the neck, forearms, wrists and hands. However, it may also occur on the scrotum, the inner surfaces of the thighs, the upper chest and back, the lower legs and around the

ankles. Hyperpigmentation and keratoses are not prominent features of this type of arsenical lesion. Patch tests have confirmed that the dermatitis is due to arsenic, not to any impurities that may be present in the crude arsenic trioxide product. Chronic dermal lesions may occur after many years of occupational or environmental exposure. Hyperkeratosis, warts and melanosis of the skin are the conspicuous signs. Melanosis is most commonly seen on the upper and lower eyelids, around the temples, on the neck, on the areolae of the nipples and in the folds of the axillae. In severe cases arsenomelanosis is observed on the abdomen, chest, back and scrotum along with hyperkeratosis and warts. In chronic arsenic poisoning, depigmentation, i.e., leukoderma, especially on the pigmented areas, commonly called "raindrop" pigmentation, also occurs. These chronic skin lesions, particularly the hyperkeratoses may develop into pre-cancerous and cancerous lesions.

Peripheral neuritis has been observed in survivors of acute arsenic poisoning as well as in chronic arsenic exposure. The neuritis is sensory in character and initially affects the hands and the feet. It is very similar to the sensory neuritis of chronic alcoholism. An early finding is disturbance of skin sensation and intolerance to pressure. Later when sensory perception is impaired, ataxia develops. The

sense of touch may be diminished, the appreciation of temperature and pain increased or decreased. The cranial nerves have occasionally been reported to have been involved. Motor paralyses are rarely seen and then only in the more severe cases. The first muscles affected are the extensor muscles of the feet and the extensor muscles of the hands. The differential diagnosis includes the neuritis of chronic alcoholism and plumbism. Improvement can be expected if the patient is removed from exposure.

Anemia and leukocytopenia can occur in chronic arsenic poisoning. Liver involvement has been observed more commonly among workers with a history of chronic arsenic ingestion as opposed to those workers with a history of chronic respiratory exposure. The association of chronic arsenic poisoning and cirrhosis has been discussed frequently but has rarely been documented in the absence of a history of intake of alcohol.

There has been some doubt about the extent of involvement of the cardiovascular system as a result of chronic arsenic exposure. Arsenic is now believed by most authors to exert a direct toxic action on cardiac muscle in chronic as well as acute arsenic intoxication. A review of the literature would support a relationship between arsenic poisoning and electro-

cardiographic changes and possible cardiac damage. Most writers believe this damage is reversible if the patient is removed from arsenic exposure.

(d) Chronic Arsine Poisoning

In the past exposure standards for arsine were designed to protect workers from the acute effects of exposure to arsine. Chronic inhalation of arsine in concentrations below those required to produce acute toxicity may be widespread in modern industry.

It is believed that inhaled arsine is rapidly absorbed from lung tissue (Pershagen, 1982) and is oxidized to form elemental trivalent arsenic and arsenic trioxide. Trivalent arsenic compounds are believed to be carcinogenic.

(e) Suppression of Immunity

Increased incidence of herpes simplex and decreased resistance to infection have been noted in a number of subjects following accidental exposure to elevated levels of arsenic. (Reynolds, 1901). This and other similar incidents have aroused interest in the relationship between arsenic exposure and the immune response.

Research by Gainer and Pry (1972) showed that

virus infected mice treated with large doses of arsenicals had higher mortality rates than untreated controls, and this increased mortality was related to the mouse's impaired ability to resist viral disease. The exact mechanism of this phenomenon is not known, however, it is suspected that large doses of arsenic decrease the production of interferon, or, decrease the activity of interferon. In these experiments arsenical treatment consisted of injected doses of sodium arsenite at the time of inoculation with virus or administering sodium arsenite or 3-nitro-4-hydroxyphenylarsonic acid at rather high concentrations of arsenic (75-150 ppm) in the drinking water for various periods before or after inoculation. The doses of arsenic used in these studies were such that any relevance to human data would be limited to situations involving extreme exposure to arsenic such as accidental spills. The second observation drawn from Gainer's experiments is the possibility that in very low doses arsenic appeared to increase the antiviral activity of interferon. This could provide the rationale behind the beneficial "growth-promoting" effects of arsenical feed additives for livestock and perhaps for the medicinal use of arsenic in Fowler's solution in the early years of this century.

There have been no laboratory studies on the effect of arsenic on immunity in humans. It is a

subject of great interest because of the association of arsenic with cancer and the possible role of the immune response in protecting the body against cancer. Any conclusions regarding the possible effects of low concentrations of arsenicals on the ability of humans to resist disease must await further research.

(f) Teratogenesis and Mutagenesis

There have been a number of experiments on the teratogenic effects of arsenic in animals.

Ferm et al (1968, 1969, 1971) demonstrated a high incidence of dead, resorbed and malformed embryos in pregnant hamsters given intravenous injections of sodium arsenate. The developmental malformations resulting from the injection of sodium arsenate varied with the time of injection during the critical stages of embryogenesis. The spectrum of malformations included anencephaly, renal agenesis and rib malformations. It was shown that the incidence of malformations and resorptions could be decreased by the administration of sodium selenite with sodium arsenate.

Hood and Bishop (1972) gave intraperitoneal injections of 45 mg/kg of sodium arsenate to mice. This had the greatest effect on the 9th day of gestation with up to 60% of the embryos dead, resorbed or malformed. The teratogenic effect of sodium

arsenate was counteracted by early intraperitoneal injections of British Anti-Lewisite (B.A.L.). Beaudoin (1974) injected pregnant Wistar rats once intraperitoneally with various doses of sodium arsenate at one of days 7-12 of gestation. He demonstrated that the embryolethal and teratogenic effects of arsenate were dose and time dependent.

Schroeder and Mitchener (1971) added 5 ppm sodium arsenite to the drinking water from weaning to death in an experiment using mice of the Charles Rivers strain. The criteria used to estimate toxicity were intervals between litters, the age at which the pair produced its first litter, the ratio of males to females, the number of runts, deaths, stillborn offspring, failure to breed and congenital abnormalities. The mice fed arsenic survived well through the third generation. The ratio of males to females increased from 0.93 to 1.71. The increase in rates of males to females may not be a true teratogenic effect. However, as some water supplies have been found to contain concentrations of arsenic comparable with that used in the experiment, this effect should be borne in mind.

Teratogenic effects have not been reported in humans. Arsenic doses in the animal experiments, cited above, with the exception of that of Schroeder and

Mitchener, were very large, beyond the level that could be foreseen in human exposures.

There are some reports on the mutagenic effect of arsenic. Chromosomal breaks have been observed in human leukocyte cultures exposed to sodium arsenite *in vitro* and in leukocyte cultures obtained after long exposure to arsenical compounds *in vivo*. (Petres et al. 1968 in National Academy of Sciences, 1977).

An increased frequency of chromosome aberrations in smelter workers has been reported by Beckman et al (1977) although, in this instance, the effect could not be attributed with certainty to arsenic as the workers were exposed to other agents.

(g) Carcinogenesis

The carcinogenic properties of arsenic in man have been suspected for a long time, however, corroborative animal data is still lacking. There is little doubt that skin cancers in man have resulted from inorganic arsenic in drugs, drinking water and the occupational environment (Tseng et al. 1968).

There have been a number of epidemiologic studies of occupationally exposed workers in which an increased incidence of death due to respiratory cancer has been demonstrated and attributed to the inhalation of

inorganic arsenic compounds.

(h) Epidemiologic Studies: Respiratory Carcinogenesis

In 1948, Hill and Faning examined the proportionate mortality of the deaths of men over age 20 who died between 1900 and 1943 and who had been employed in a factory where arsenical sheep-dip powder was manufactured. The proportionate mortality of this group was compared with the proportionate mortality of all other men over age 20 who died during the same period in the same births and deaths registration subdistrict. There were no specific exposure histories available; any person who worked in this factory and died during this period was counted and compared with the rest of the cohort which was divided into three groups on the basis of occupation; agricultural workers, general labourers and artisans, and shopkeepers. There were 75 deaths among the factory workers and 1216 deaths among the other three occupational groups. Of the factory workers 29.3% died of cancer as compared with 12.9% among the total comparison group; 31.8% of the cancers among factory workers were reported to be in the respiratory organs as compared with 15.9% in the comparison group and 13.6% of the cancers in the factory group were reported

to be skin cancers as opposed to 1.3% in the other three groups. (See Table II)

This study although based on a small sample size strongly supported the finding of an excess cancer-mortality risk among non-smelter workers exposed to arsenic. (See Table III).

In 1951, Snegiroff and Lombard failed to find an increased incidence of lung cancer among workers exposed to arsenic trioxide in the metallurgical industry. However, they did not consider the mortality experience of previous employees and further analyses revealed a sizable increase in the excess of lung cancer - (NIOSH, 1975)

In the 1950's an unusual cluster of deaths among vineyard workers in France and Germany led to an extensive autopsy series among these workers. They had been heavily exposed to arsenical insecticides through inhalation as well as ingestion of contaminated wine. Lung cancers as well as liver hemangioendotheliomas were found in about half the workers with cutaneous arsenicism or arsenic toxicity at death (Roth, 1957).

In 1963, Pinto and Bennett studied deaths amongcopper smelter workers and it was believed at that time that the frequency of deaths due to respiratory cancer had not been influenced by arsenic exposure. In

1974, a mortality study of the population in the same plant by Milham and Strong revealed 40 deaths from lung cancer - the expected number of deaths due to lung cancer was 18 (Milham and Strong, 1974).

In 1969, Lee and Fraumeni studied the mortality experience of 8,047 white males employed at the Anaconda smelters during the period January 1, 1938 to December 1, 1963. For inclusion in the study the workers had to be employed for 12 months or more prior to December 31, 1956.

The group was categorized on the basis of exposure to arsenic and to sulfur dioxide as light, medium and heavy, and divided into five cohorts on the basis of length of employment. Their findings indicated an increased mortality in the total group when compared with the white male population of the same U.S. states. The incidence of death due to respiratory cancer was found to be significantly in excess of expectation in each cohort - the observed to expected mortality from respiratory cancer being approximately 7, 5 and 2.5 in the heavy, medium and light arsenic exposure groups. No smoking histories were available, however, there is no reason to believe the smoking habits of this population differed from that of the rest of the white male population of the same states.

This study supported the belief that inhaled

inorganic arsenic is a respiratory carcinogen in man but did not rule out the influence of sulphur dioxide or other unidentified chemicals (Lee and Fraumeni, 1969).

The finding of an excess lung cancer mortality is of great significance as this study meets most of the criteria of an ideal epidemiological study. The population at risk was followed for a significant period of time, the size of the population was large enough to provide a high degree of statistical power and to allow a breakdown into large exposure categories.

The Lee and Fraumeni study was updated by Lubin, Pottern, Blot, Tokudome, Stone and Fraumeni (Lubin et al. 1981). The Lee and Fraumeni 1969 paper examined the mortality of smelter workers during the period 1938 through 1963. Lubin et al examined the mortality data from 1964 through 1977.

A total of 1628 deaths were identified in the cohort during the years 1964-1977. This number was significantly greater than the expected number, SMR = 127 ($p < 0.001$). Significant excesses in mortality were found for malignant neoplasms.

Relative risks of death from the selected causes were calculated from the multivariate model, according

to total length of employment in the smelter and in work areas with heavy or medium concentrations of arsenic (Table IV). There was an increased risk of respiratory cancer associated with medium or heavy arsenic exposure in all duration-of-employment groups ($p \leq 0.01$). After adjusting for total length of employment, the risk for men working more than four years in areas with high or medium arsenic exposure was nearly double that for those never working in these areas. In contrast, the other causes of death with elevated SMRs were unrelated to arsenic level.

Although mortality from respiratory cancer was greatest in workers with high and medium arsenic exposures, the authors stated that elevated risks were also associated with work for 25 or more years in areas of the smelter with low exposures to arsenic (no data given in the paper). The authors state that the excess mortality from respiratory cancer among those employed at the smelter for less than five years, was primarily related to the higher proportion of time that these workers spent in areas with heavy or medium arsenic exposure.

Lubin et al concluded that this study cohort continued to demonstrate an excess risk of respiratory cancer.

Lee-Feldstein (1981) updated the mortality study

of Lee and Fraumeni to 1977. This study reports the complete mortality and exposure experience during 1938-1977 of the Anaconda copper smelter workers employed at least 12 months before December 31, 1956. The study cohort is composed of 8045 white males and the comparison population was made up of white males in the states of Idaho, Wyoming and Montana whose age, calendar period and cause-specific mortality rates during 1938-1977 were the basis for generating expected numbers of deaths. Of the thirteen causes of death considered there was a significant increase in mortality for respiratory system cancer, (SMR-285) as well as cancer of the digestive system, diseases of the heart, emphysema, tuberculosis, vascular lesions of the central nervous system, and cirrhosis of the liver. When the causes of death were analyzed further by length of employment group, respiratory cancer was found to be significantly in excess of expected in each group. Respiratory cancer SMR's increased with length of employment (in agreement with the earlier Lee and Fraumeni study (see Table V).

Lee-Feldstein concluded that the excess in respiratory cancer deaths observed in her study is most likely related to exposure to carcinogenic agents in the workplace and that this study supports the hypothesis that arsenic is a respiratory tract carcinogen among various occupationally exposed

groups. The author admitted that it is possible that other agents in the smelter such as sulphur dioxide may enhance the carcinogenic effect of arsenic.

Higgins (Welch, Higgins et al. 1982) established a new cohort of 1800 men drawn from the original Lee and Fraumeni cohort. This group included all the men in the heavy exposure category (at least 24 months in the arsenic kitchens, Cottrells or arsenic roasters) and a 20% random sample of the rest of the group. Their vital status was established to 1978.

Arsenic exposure was based on available industrial hygiene data collected by the company and from three surveys conducted by the State of Montana between 1943 and 1965. 818 samples of arsenic in air had been taken during that period and measurements were available in 18 of 35 smelter departments used in this analysis. Where measurements had been made an arithmetic average concentration was calculated and multiplied by an exposure factor developed by the Industrial Hygiene Department to allow the calculation of an 8-hour average exposure. Concentrations for departments that were not sampled were estimated from those that were known. Departments with similar average arsenic concentrations were combined into four broad categories:

1. low ($<100\ \mu g/m^3$)

2. medium (100-499 $\mu g/m^3$)
3. high (500-4999 $\mu g/m^3$)
4. very high (>5000 $\mu g/m^3$)

Three indices of arsenic exposure were developed for each man based on his work history and industrial hygiene data.

1. Time Weighted Average (TWA) - An estimate of each man's average daily dose rate calculated by multiplying the time spent in each department by the estimated concentration for that department. This was calculated at two points in time for each man, 1) when he entered the cohort (in 1938 if he had worked one year or more before that, or after completing one year of work in the smelter), and 2 at the end of the Lee and Fraumeni follow-up in 1964.

2. Ceiling or Peak Exposure for 30 Days - This index was based on the highest arsenic exposure category in which a man had spent at least 30 days.

3. Cumulative Lifetime Exposure ($\mu g/m^3$ yr) - This was a man's total lifetime arsenic exposure and then adding all the arsenic concentration years

together.

TWA & Ceiling Groups:

<100 $\mu g/m^3$

100-499 $\mu g/m^3$

500-4999 $\mu g/m^3$

≥5000 $\mu g/m^3$

Cumulative Groups:

500 $\mu g/m^3$ years

500-2000 $\mu g/m^3$ years

2000-12,000 $\mu g/m^3$ years

≥12,000 $\mu g/m^3$ years

Mortality

Mortality for specific cause of death by sample stratum is shown in Table VI. ((1) Heavy, (2) Other). SMR's were significantly elevated in both strata for all causes of death; all malignancies, respiratory cancer, heart disease, ischemic heart disease.

For each of these causes of death the SMR among men in the "Heavy" category was greater than that for men in the "Other" category.

Mortality from those causes of death which were apparently related to the initial arsenic categories (Table VI) are shown in Table VII.

Analyses by TWA showed SMR lowest in the lowest exposure category and highest in the highest. The increasing trend was most consistent for respiratory cancer and also had the steepest gradient with a roughly seven fold excess in the highest exposure category.

Analysis by ceiling arsenic categories produced a different pattern. The SMR's for the men in the low and medium ceiling categories were not significantly elevated while the SMR's in the high and very high categories ($\pm 500\ \mu g/m^3$) were elevated. (Table VII)

The authors concluded that the ceiling level of arsenic is more significant than the TWA, (Table VIII). The number of deaths in each of the Low and Medium categories are too small to be statistically valid and this conclusion is difficult to accept.

Cumulative Arsenic Analysis

Mortality as a result of respiratory cancer by categories of cumulative exposure to arsenic show that the SMR increases as the cumulative arsenic exposure increases. Men whose cumulative lifetime arsenic was below 500 $\mu g/m^3$ years did not have an elevated SMR. (Table IX). On the basis of this table, it was concluded that the cumulative or total arsenic exposure was a more significant factor in the production of an increased risk for respiratory cancer than was the number of years worked.

This paper examined the relationship between the estimated sulphur dioxide exposure categories and respiratory cancer mortality. Again the possible role of sulphur dioxide in the production of these cases could not be ruled out.

The epidemiologic studies of Lee and Fraumeni, Lubin, Lee-Feldstein and Higgins all represent excellent studies of the mortality experience of Anaconda Smelter workers. Although there were

methodological differences, the authors all concluded that their studies supported the hypothesis that arsenic is a respiratory carcinogen. A dose-response relationship was found which showed that increasing exposure to arsenic was correlated with increasing lung cancer risk.

The studies by Lee and Fraumeni and Lee-Feldstein included the complete original cohort (all workers with 12 months of employment prior to December 31, 1956) and the Lee-Feldstein study covered the mortality experience up to the end of 1977 which allowed all of the cohort at least 20 years of latency since their first exposure.

The study by Higgins included an extensive estimation of exposure for the cohort but the arsenic in air measurements which were the basis of this estimation, were incomplete. They would appear to be the best data available; whether they are truly representative of the exposure of these workers can be questioned. A second problem with the study by Higgins is that it examined only 20% of the original cohort which were designated as having arsenic exposures "other than heavy" by Lee and Fraumeni. As a result, this study has a low statistical sensitivity for the detection of an excess risk of respiratory cancer among this group. Analysis of the study suggests that

Higgins et al using Method I had less than a 37% chance of detecting a 1.5 fold respiratory cancer risk in the two lowest Ceiling categories (≤100 $\mu g/m^3$ and 100-500 $\mu g/m^3$). For the TWA category of less than 100 $\mu g/m^3$ the statistical power has been estimated to be 31%.

Although the authors propose that there is a threshold for respiratory carcinogenesis as a result of exposure to arsenic the conclusion does not stand up to scrutiny. The report suggests that if the workers are not exposed to arsenic in air levels in excess of 500 $\mu g/m^3$ (0.5 mg/m^3) there would be little excess incidence of respiratory cancer. In the next sentence they remind the reader to interpret these results with caution as they are based on estimated department averages rather than on measured concentrations for individual jobs. None of the other studies of arsenic exposed populations demonstrate a threshold.

If the cumulative exposure data in this study is examined a significantly increased respiratory cancer mortality is observed among workers in the 500-2000 $\mu g\ As/m^3$ years category. The average of this group 500-2000 is 1250 $\mu g\ As/m^3$ years. Assuming a worker could be exposed for 45 years, this would limit his average occupational exposure to a level of 28 μg arsenic per cubic meter of air.

Pinto, Varner et al (1976) reported the results of

a study of the relationship between airborne arsenic trioxide and urinary arsenic. A total of 24 workers participated in this study, for which they wore personal air samplers and did not wear respirators for 5 successive days. Workers were asked to not eat fish for 2 days preceding and during the study period. Pinto et al stated, "A fairly good correlation was found between airborne arsenic concentrations and urinary arsenic levels over the range studied." The conversion factor was 0.304, a urinary level of 100 µg/L of arsenic was roughly equivalent to 30.4 µg As/m^3 air.

Pinto, Enterline and Henderson (1977) reviewed the mortality experience of 526 men previously employed in the ASARCO copper smelter at Tacoma. This cohort was made up of retirees. To be eligible for the cohort they had to be alive as of January 1, 1949 and had to have reached age 65 by December 31, 1960. The mortality experience was observed for the period 1949-1973.

Expected numbers of deaths were generated from age-specific and cause-specific mortality rates for white males in Washington State during 1949-1973.

Arsenic exposure indices were developed for each man using estimated urinary arsenic levels (on the basis of plant experience, a typical urinary arsenic

level for each area was determined).

The average urinary arsenic value for a department as determined in 1973 was multiplied by the time in years that a retiree had spent in that department; for each man the same calculation was made for each department in which he had worked and the sum of these calculations was made. This was called the man's exposure index. This exposure index when divided by the total number of years worked by the retiree is a figure which represents the intensity of the retiree's lifetime exposure to arsenic. These indices are not a measure of intensity, only an index for comparison purposes.

The authors then examined the observed deaths at age 65 and over for this cohort of 527 men and it was shown they had an SMR for all causes of 112.2, an SMR for all types of cancer of 148.4, and an SMR for respiratory cancer of 304.8. The expected mortality was based on the experience of the male population living in the State of Washington in the time interval which characterized the study population. (See Table X).

Standardized Mortality Ratios (SMR's) were then calculated for groups of workers categorized by duration of employment, total exposure and average exposure. (Table XI and Table XII).

If the mean exposure index in Table XI is plotted against SMR in Table XI, there is a roughly linear trend.

The authors then examined duration and intensity of exposure and came to the conclusion that both duration and intensity of exposure contribute to the excess respiratory cancer, although intensity of exposure would seem to be a better predictor of respiratory cancer than duration of exposure.

They suggest that a threshold of safety for arsenic trioxide may exist based on the observation of an SMR of 95.2 for retirees exposed for less than 25 years with an intensity of exposure to arsenic of less than 200 μg/L urine. (Table XII). There were only 2 deaths in this group level.

Enterline and Marsh (1982) conducted a study of the mortality experience of 2802 men who worked one year or more during the period 1940-1964 at a copper smelter in Tacoma, Washington (ASARCO). Pinto, Henderson and Enterline (1978) had previously examined the mortality experience of retirees from the same smelter. In this study urine arsenic levels determined in 1973 were used to characterize the arsenic exposure by department. In the 1982 study (Enterline and Marsh 1982) estimates of historic arsenic exposure were made and the arsenic exposure indices were revised to better

reflect the true exposure of the workers being assessed. As of December 31, 1976, 1061 deaths were known to have occurred; 1690 were known to be alive and the vital status of 51 was unknown.

The mortality experience of the study population was examined during the time interval January 1, 1941 to December 31, 1976 and compared with the mortality experience of the U.S. white male population as well as the white male population of the State of Washington. For each man a cumulative arsenic exposure index was found by multiplying the estimated urinary arsenic concentration μg As/L urine) at each job by years at that job and summing this product across all jobs. This total cumulative arsenic exposure index can be thought of as μg As/L urine-years. The average intensity of exposure is a time weighted measure expressed as μg As/L urine and is found by dividing the cumulative exposure index by the duration of exposure.

A complex method was adopted to produce an effective cumulative exposure by applying a scheme to discount exposures which were unlikely to be related to the development of disease. This resulted in three figures for each worker - the average urinary arsenic level, the cumulative (total) arsenic level and the cumulative arsenic level minus 10 years of exposure preceding death or the study cut-off date. This was

done on the theory that the exposure immediately preceding death from lung cancer would not have been responsible for the death because of the latency period between the onset of exposure and death due to respiratory cancer.

The period of observation of mortality was 1941-1976. The overall mortality (compared with white males in the State of Washington) was slightly elevated, cancer mortality was significantly elevated ($p \leq 0.01$) due mainly to cancer of the respiratory system. Table XIII shows deaths and SMR's for cancer by type (site) of cancer using both comparison populations. The respiratory cancer SMR's for the study cohort was 198.1 (Washington State) and 189.4 (U.S.).

Table XIV shows the relationship between respiratory cancer and cumulative arsenic exposure lagged zero years and lagged 10 years. Although no obvious relationship between risk and exposure is apparent careful statistical analysis shows that the data in both categories are consistent with a dose-response function.

This would support the assertion that an increased respiratory cancer risk can be seen in these workers. Using a urine to air conversion factor of 0.3 (Pinto, Varner et al 1976) 500 µg As/L years = 150 $\mu g/m^3$ years;

the mean of the class interval 302 µg As/L urine years = 90 µg As/m^3 years. This dose could be accumulated by one year of exposure at 90 µg/m^3 or by more years of exposure at lower levels (i.e. 10 years at 9 µg/m^3).

Enterline and Marsh re-examined the data in a second way by following workers from their point of termination or retirement. Workers still employed when follow-up ended (Dec. 31, 1976) are not included. This is the mortality experience for a group of workers after they leave employment and includes workers who terminate because of respiratory cancer. Where the date of termination and the date of death are the same, these workers made no contribution to the person-year count. The workers are grouped by their average intensity of exposure during employment as low or high. (Table XV).

The authors state that Table XV shows that both duration of exposure and intensity of exposure contribute to cancer mortality. They freely admit that the inclusion of workers who terminate employment because of respiratory cancer may introduce a bias as in these cases death determines the dose duration rather than dose duration determining death. Of the 104 respiratory cancer deaths, 21 terminated at death and 17 deaths occurred within 5 years of termination.

Respiratory cancer SMR's in the "low" average

exposure group (defined as having an average less than 290 µg As/L, with a group mean of 163 µg As/L) ranged from 169.9 to 302.0. The respiratory cancer excesses observed in the low average exposure group were statistically significant, except for workers with less than 10 years of exposure. Using a urine to air conversion factor of 0.304; 163 µg As/L is equivalent to 49 µg As/m^3 air.

Enterline and Marsh reached the following conclusions:

(1) Concerning the relationship between arsenic and respiratory cancer, "the carcinogenic response apparently can occur rather quickly - in this study apparently in about 10 years".

(2) The carcinogenic effects of arsenic appeared to decline with time following the cessation of exposure.

(3) Arsenic appears to act as a cancer promoter rather than an initiator, based on the epidemiological evidence of lack of an effect of latency and based on the apparent decline in risk after cessation of exposure.

A very significant study was carried out by Ott, Holder and Gordon in 1974. These authors examined the mortality experience of 173 decedents exposed to inorganic arsenic compounds in the production of insecticides, and compared it with that of 1809 decedents not exposed to those compounds. The decedents were divided into 4 groups on the basis of 8 hr. T.W.A. concentration of arsenic in mg/m^3. (See Table XVI). This was a study of workers previously employed by the Dow Chemical Company.

According to the study report, the dry arsenicals to which the workers were exposed were the following listed in order of decreasing production: lead arsenate (59 per cent), calcium arsenate (34 per cent), copper acetoarsenite (5 per cent) and magnesium arsenate (2 per cent). It is important to note that 95% of this exposure is to inorganic pentavalent arsenic compounds.

This study compared the proportionate mortality rate of arsenic-exposed employees with that of non-exposed employees over a 37-year period (1919-1956). The "exposed" group included those workers who had spent 1 or more days in the arsenical production area, while the "control" group had never worked in the arsenic exposure area.

To allow for differences in duration of exposure, dosage of arsenic was calculated according to the

following formula:

Dosage in milligrams = $(D_i\ T_i)\ B$

where i represents the arsenic exposure group; D_i, the number of working days each worker spent in the ith exposure group category (21 working days/month); T_i, the time-weighted average (TWA) concentration of arsenic for an 8-hour day in the ith exposure group; and B, four cubic meters of air ($\mu g/m^3$) as the average respiratory volume assumed for an 8-hour day/worker. Results were expressed in the natural logarithm ($\log_e$) of the dosage in milligrams.

It should be noted here that an estimated respiratory volume of 4 $\mu g/m^3$ air for an 8-hour working day is lower than is normally chosen. It is more usual to assume a respiratory volume of 10 $\mu g/m^3$ air for an 8-hour working day. The authors discussed the fact that this figure reduces the estimated arsenic exposure. It is also believed that the estimates of arsenic in air measurements that were used to make the calculation above were much lower than were actually present at the time the workers were exposed.

An increased percentage of cancer deaths was observed among the exposed group (32.9 per cent versus the non-exposed 20.7 per cent). The authors' analysis of the data indicated an approximate three-fold increase in lung cancer for the exposed population (16.2 per cent) over the non-exposed (5.7 per cent).

To supplement the results of the first analysis, they performed a cohort analysis by examining mortality data for 603 men who had worked for at least 1 month in

the exposure area. They observed 35 cancer deaths among the exposed group versus 19.4 deaths expected, on the basis of the U.S. white male age-calendar, time-cause specific rate. Of the 35 total cancer deaths among the exposed population, 20 lung cancer deaths were observed where only 5.8 would have been expected. The results of the cohort analysis confirmed the finding of an excess respiratory cancer mortality.

Of interest was the fact that of 173 deaths recorded for workers in the exposed population, 138 of the workers had worked in the exposure area for a period of less than 1 year, and of these 138, 16 died of lung cancer.

The observed vs. expected deaths due to respiratory cancer by exposure category are shown in Table XVII and it would appear that a dose-response relationship can be demonstrated.

This project was assessed by Blejer and Wagner (1976). They attempted to estimate the daily 8 hour time weighted average arsenic concentrations that each of these levels would represent if it is assumed that the dosage for each category was absorbed over a 40-year work life. They did this by converting the dosage categories in Table XVII from logarithmic to arithmetic units and dividing each by the estimated 40 year respiratory volume (4 m^3/day x 21 days/month x 12

month/yr.x 40 yrs.= 40,320 m^3) and expressing the result in micrograms per cubic metre.
(Table XVIII).

From this table, the authors concluded that the no-effect level (no increase in the risk of respiratory cancer) for an occupational exposure, is in the very low (less than 3) micrograms per cubic meter range.

It is recognized that this study could be criticized on the basis that the number of cases in each cell is too small, however, it was the best available information at the time.

According to the original report prepared by Ott, Holder and Gordon, 95 per cent of the inorganic arsenic compounds to which the workers in this study were exposed were pentavalent. Therefore, the epidemiological evidence in this study would support the conclusion that inorganic pentavalent arsenic compounds must be considered to be carcinogenic.

A cancer mortality study was carried out by Mabuchi, Lillienfeld and Snell (1979). They examined the vital status of 1393 persons exposed to high air concentrations of inorganic arsenic during the manufacture and packaging of pesticides at a plant in Baltimore. (Allied Chemical Plant).

These workers were exposed to both inorganic

arsenicals and non-arsenical compounds. It is reported that most of the inorganic arsenic compounds in this study were trivalent.

The follow-up on the female portion of the cohort was poor (66.8% of 343 women) and no statistically significant increases in morbidity were observed. They then studied the male portion of the cohort.

The males in the cohort had a statistically significant lung cancer SMR 168, when compared with Baltimore City white males; and 265 when compared with U.S. white males.

A strong gradient of lung cancer risk with increasing duration of exposure was observed (see Table XIX) and a dose-response relationship was postulated on the basis of this table.

Mabuchi et al did not have smoking histories for the cohort members, however, it was considered unlikely that smoking could account for the excess of lung cancer noted as other smoking related diseases were not noted to be in excess.

It was Mabuchi, Lillienfeld, and Snell's conclusion that their findings provided strong evidence for a causal relationship between occupational exposure to inorganic arsenicals and lung cancer.

Risk Assessment of Lung Cancer in Relation to Inhalation of Arsenic

The previous sections show that arsenic is a proven human carcinogen and that there is no good evidence for a threshold level of exposure. Consequently the only level of exposure which is guaranteed to protect the worker against the risk of lung cancer due to exposure to arsenic in the workplace is zero. If zero exposure cannot be achieved, some level of risk due to exposure to arsenic in the workplace will result and it is possible to calculate the approximate amount of risk due to various levels of exposure.

As already noted, Enterline and Marsh (1982) in a study of workers exposed to arsenic in a copper smelter reported Standardized Mortality Ratios for lung cancer in relation to several levels of an index of exposure to arsenic in air. The study group consisted of 2802 men who worked in the smelter for one year or more during the period 1940 to 1964. Enterline and Marsh also reported the mortality of 528 men who retired from the smelter after 1941. Some of the workers may have been exposed to arsenic as early as 1913, when the smelter began operations. The period of observation for mortality was 1941 to 1976. This particular study

contains the most accurate exposure data of all the available mortality studies of workers exposed to arsenic in air.

Pinto, Enterline and Henderson (1977) show that the risk of lung cancer increases as the duration of exposure increases and as the intensity of exposure, as indicated in the arsenic content of urine, increases. (See Table XI). An exposure index was calculated for each worker using the time employed in various departments of the smelter and the arsenic content of urine of men working in these departments. The index was expressed in units of μg As-years of exposure to arsenic per litre of urine. The surveys of urinary arsenic levels began in 1948, and urinary arsenic levels before 1948 were estimated to be the same as those found in the period 1948-1952. Because the surveys show that urinary arsenic levels were dropping between 1948 and 1975 and this trend probably started before 1948, the estimated urinary arsenic levels for the years before 1948 are probably too low.

In order to fit a risk-exposure function to these data, it was assumed that the number of lung cancer cases attributable to airborne arsenic is linearly related to the product of the "expected" number of lung cancer deaths in the population and the arsenic exposure index. This is a relative risk model and it

is important to note that this model predicts that the number of lung cancer cases attributable to exposure to arsenic increases with both increasing arsenic exposure and increasing lung cancer risk due to other carcinogens. Enterline and Marsh used the mortality rates in the general population of white males in the State of Washington to calculate the "expected" number of lung cancer deaths. Other factors such as smoking may account partially for the differences in lung cancer risks observed in the smelter workers and the white male population of Washington State. In order to attempt to take these other factors into account, it is assumed that some of the observed increase in lung cancer risk may be independent of the level of arsenic exposure. It may also be true that in the smelter environment, exposure to arsenic may be correlated with exposure to other agents which increase lung cancer risk, and if that were true, the following calculations, in the absence of any other biases in the data, would result in an over-estimate of the risk attributable to exposure to arsenic.

Figures 1 and 2 show graphically the data used to calculate the risk-exposure function as well as the risk-exposure function which "best" fits the data. The observed number of cases in each exposure class was assumed to be an observation from a Poisson distribution with mean, $(A + 1) \times E + B \times I \times E$ where A

is the estimated relative increase in the expected lung cancer risk which is independent of the level of arsenic exposure, E is the "expected" number of deaths in the exposure class, and B is the estimated relative increase in the lung cancer risk (relative to the "expected" lung cancer risk) per unit increase in the arsenic exposure index, and I is the exposure index (μg As-yrs/L urine). The Statistical Analysis System (SAS 1979) was used to do these calculations.

In both sets of data, a linear risk-exposure function fits reasonably well to the data. For the data observed in the whole study population using the ten year lag model, there is an increase in the lung cancer risk which was independent of arsenic exposure relative to white male residents of Washington State (RR = 1.63, P = 0.04) and the relative increase in lung cancer risk per unit of exposure to arsenic was estimated to be 5.9×10^{-5}/μg As-yr/L urine (P = 0.002). For the data observed in the retirees, the risk function showed an apparent threshold. The estimate of the relative risk which was independent of arsenic exposure was 0.10 (P = 0.005) and the relative increase in lung cancer risk per unit of exposure to arsenic was calculated to be 3.0×10^{-4}/μg As-yr/L urine (P = 0.01). It should be pointed out that these calculations using the data observed in retirees is highly influenced by the "expected" number of cases in

the exposure group 3000-6000 µg As-yr/L urine and less so by the results at higher levels of exposure. It should also be pointed out that if the intercept term A were omitted the calculated risk factor would have increased to 1.1×10^{-4}/µg As-yr/L urine for the whole study population and decreased to 1.6×10^{-4}/µg As-yr/L urine in retirees.

Table XX shows the numerical data which were used to calculate the risk-exposure function and its estimated parameters. Based on these calculations, exposure for one year to elevated levels of arsenic in air which increase the arsenic content of urine by 1 µg/L increases the usual lifetime risk to dying of lung cancer by a factor of 1.00006 (0.006%) based upon the data obtained from the entire study population and 1.0003 (0.03%) based upon data observed in retired smelter workers.

Biases and uncertainties in various components of the data used to calculate the parameters of the risk-exposure function affect the precision of the estimates of the health effects associated with a given level of exposure to airborne arsenic. It is extremely difficult to estimate confidence intervals for these estimates with the data available. It is however, noteworthy that the calculations based on data obtained in similar ways by the same investigators result in two

risk estimates which differ by a factor of five. More precise estimates of the risk attributable to a given level of exposure to arsenic cannot be made with the data presently available.

Depending upon the particle size of the airborne arsenic an increment of 1 μg arsenic per cubic meter of air in the workplace increases the content of arsenic in urine by between 0.3 and 1.5 μg per litre (see footnote). In comparison, Pinto, Enterline, Henderson and Varner (1977) have found that 1 μg As/m^3 in air increases the arsenic content of urine by 3.3 μg/L and if this conversion factor were used, the number of lung cancers attributable to arsenic exposure would have been increased by a factor of 3.3. More recent work by Carlsson (1976) and Buchet, et al. (1981) have produced very similar conversion factors if the variations in protocol used in these studies are considered. Table XXI shows the calculation of the mortality due to exposure to arsenic in the workplace. Various approximations each with different effects were used in the calculation of risk. The calculation used a model where the lung cancer risk due to exposure to arsenic increased immediately following exposure and persisted for the remaining lifespan. This aspect of the model may lead to an overestimate of the mortality due to exposure. In this model it was assumed also that the risk due to arsenic exposure occurs in proportion to

the level of lung cancer risk which would exist in a population not exposed to arsenic. This is known as the relative risk model. The calculation did not adjust the population size at each age for the effects of earlier mortality due to arsenic exposure and the effect of this approximation is that the calculated value overestimates the actual mortality due to arsenic exposure. Mortality rates in the general population are usually higher than mortality rates in a working population and the effect of the use of the general population data in the calculation is that the risk attributable to arsenic exposure in a working population is underestimated. The calculated values should be viewed as approximations for the effects of arsenic exposure in a working population.

Table XXII shows the results of the calculation of mortality attributable to arsenic exposure when the data from two study populations are fitted to two different forms of risk exposure functions and four different ratios are used to convert the arsenic content of urine to the arsenic content of air in the workplace. When 10,000 workers are exposed continually to 10 ug As/m^3 of air, the number of lung cancer cases occurring per year because of the arsenic exposure is calculated to be between 0.09 and 5 and a representative value of 2 lung cancers per year due to arsenic exposure is used. If the exposure level were 1

μg As/m^3, the number of lung cancer cases due to arsenic exposure would be about 0.2 per year per 10,000 workers and if the exposure level were 100 ug As/m^3, the number of lung cancer cases due to arsenic exposure would be about 20 per year per 10,000 workers.

As noted previously, if it is not possible to achieve a zero level of exposure to arsenic in the workplace, some amount of risk, dependent upon the level of exposure will likely result. In the case of radiation workers, the maximum risk resulting from exposure to the annual occupational whole body exposure limit for a radiation worker for a working lifetime can be inferred to be $5x10^{-4}$ per year (5 cases per 10,000 workers per year) (ICRP 1977a). In groups of workers where the annual occupational whole body exposure limit of 50 mSv (5 rem) has been applied, ICRP has found that the annual exposures of individual workers fit a lognormal function with a mean of 5 mSv and with very few values approaching 50 mSv. Consequently, the average annual risk to the workers is at most $5x10^{-5}$ per year (0.5 cases per 10,000 per year) when the annual individual exposure limit is 50 mSv. ICRP compares this risk with mortality rates due to accidents in the workplace found in other industries and occupations. Tables XXIII and XXIV show the accidental injury death rates in various occupations in the United States (ICRP 1977b) and in Ontario (ACOHOS

1983). These data show only occupational mortality mainly due to accidental injuries and exclude occupational mortality due to other causes of death such as cancer, and consequently these values underestimate the amount of occupational mortality.

The tables show a range of occupational mortality from a low of 0.2 per 10,000 workers per year to 14.8 per 10,000 workers per year and it appears that the level of occupational mortality in a given industry is somewhat consistent from year to year.

Another measure of the occupational risks faced by workers is the loss of life expectancy due to occupational hazards. Causes of death which are more frequent in younger age groups result in a greater loss of life expectancy even if the mortality rates averaged over a lifetime are the same. In this regard, cancers tend to appear more frequently in older age groups while accidental occupational mortality rates appear to be approximately constant after the age of 30 with the rates in younger men being lower (ICRP 1977b). Table XXI compares the life expectancy lost due to exposure to arsenic and due to accidents in the workplace, when the overall average rates for these two hazards are the same. The calculations show that each lung cancer case caused by arsenic exposure loses approximately 12 years of life while each accidental fatality in the workplace

loses approximately 33 years of life.

There are aspects to the perception of risk such as the attitude that deaths due to cancer are "worse" than a sudden death such as death due to a heart attack or an accident. (Whyte 1983). Individuals will also voluntarily expose themselves to greater risks than they would have imposed on them. For example, a man might choose to smoke cigarettes with an average annual lung cancer risk of more than 10^{-3} and yet refuse to work in an industry where the fatality rate is 10^{-4} per year.

One approach to the setting of occupational exposure standards is to set the level of exposure so that the resulting total amount of risk from all the hazards in the workplace is comparable to the risks observed in occupations which are at the lower end of the range of risks observed in various occupations.

Footnote

Table XXV shows the data concerning intakes and losses of arsenic in Reference Man. (ICRP, 1975). These data can be used to estimate the relationship between arsenic in air and in urine.

Let A_a = concentration of arsenic in ambient air($\mu g/m^3$)

A_w = concentration of arsenic in air in the workplace ($\mu g/m^3$)

f_{ab} = fraction of arsenic in air absorbed into blood through the lung

f_{bu} = fraction of arsenic in blood distributed to urine

A_u = concentration of arsenic in urine ($\mu g/L$)

Based upon data for Reference Man, the daily output of urine is taken to be 1.4L and the daily amount of air inspired is taken to be 23 m^3 of which $10m^3$ are inhaled while in the workplace.

From Table XXV, it appears that 5% of the arsenic taken into the body in food and fluids is excreted in the urine.

Assuming that there are 5 working days per week, the amount of arsenic reaching the urine from food, fluids and inhaled air is calculated to be -

$$1000 \text{ ug/day} \times 0.05 + f_{ab} \times f_{bu} \times \left(23 \text{ m}^3/\text{day} \times A_a \times \frac{2 \text{ days}}{7 \text{ days}}\right.$$

$$\left. + \frac{5 \text{ days}}{7 \text{ days}} \times 13 \text{ m}^3/\text{day} \times A_a + \frac{5 \text{ days}}{7 \text{ days}} \times \frac{10 \text{ m}^3}{\text{day}} \times A_w\right)$$

$$= 50 \text{ ug/day} + 15.86 \, f_{ab} \, f_{bu} \, A_a \frac{\text{ug}}{\text{day}} + 7.14 \, f_{ab} \, f_{bu} \, A_w \frac{\text{ug}}{\text{day}}$$

The air to blood fraction depends upon the particle size of the inhaled arsenic particles. Arsenic trioxide is a Class W compound (i.e. cleared

from the lung in weeks rather than days or years) according to the Task Group on Lung Dynamics, (Baty, Fish et al 1966). Tables XXVI and XXVII show the calculation of the air to blood fraction for various aerodynamic diameters. It appears that, depending upon particle size, the value of f_{ab} ranges between 0.06 and 0.3. The value of f_{bu} is very nearly 1.

Hence, an increment of 1 $\mu g/m^3$ in the arsenic content of air in the workplace results in an increment in the daily output of arsenic in the urine of between

$7.14 \times 0.06 \times 1 = 0.43$ µg/day

and

$7.14 \times 0.3 \times 1 = 2.14$ µg/day

This increment in the output of arsenic in the urine corresponds to an increment of between

$0.43/1.4 = 0.31$ µg/L and

$2.14/1.4 = 1.53$ µg/L

in the concentration of arsenic in urine.

Summary

There is a wealth of information available on the effects of inorganic arsenic on man and his environment but very little quantitative material on the effects of long term exposure to low levels of airborne arsenic.

Large doses of arsenic can be fatal to man, animals and vegetation. Smaller doses of arsenic

produce recognizable effects in skin and mucous membranes, gastro-intestinal, cardiovascular and neurological systems. There is impressive evidence that arsenic is a carcinogen in man.

Skin cancer has been associated with exposure to inorganic arsenic compounds in medicines, well water and pesticides.

Death as a result of cancer of the respiratory system has been attributed to exposure to airborne arsenic in non-ferrous metallurgical smelters and as a result of exposure in the use of, and the production of, arsenic containing pesticides.

There are a number of epidemiological studies involving occupational exposure to arsenic and increased risk of respiratory cancer which are of particular interest because of their quality.

In 1969 Lee and Fraumeni carried out a mortality study on 8047 white male workers exposed to arsenic trioxide while working in the smelters of the Anaconda Copper Company. In the opinion of the authors this study supported the belief that inhaled inorganic trivalent arsenic is a respiratory carcinogen in man but, they could not rule out the influence of sulfur dioxide or other unidentified chemicals in the workplace.

Lubin et al (1981) updated this study of Anaconda workers and followed their mortality experience from 1938 through 1977. The authors concluded that the workers at the Anaconda Smelter continued to have an excess risk of respiratory cancer and that a dose-response relationship was shown between arsenic exposure and lung cancer risk. This same study cohort was updated by Lee-Feldstein (1981, 1982) and the conclusion reached was that the excess risk of respiratory cancer deaths was still apparent, and that this increased risk was related to exposure to inorganic trivalent arsenic in the workplace, but that other agents in the smelter such as sulphur dioxide might enhance the carcinogenic effect of arsenic.

Welch, Higgins et al. (1982) examined a new cohort of workers drawn from the original Anaconda smelter population of Lee and Fraumeni, and established their vital status to 1978. The Higgins cohort included all the men in the heavy exposure category of the Lee and Fraumeni cohort but only a random sample of 20% of the workers in the less-exposed or "other" category. They concluded that exposure to inorganic trivalent arsenic was strongly related to respiratory cancer and also suggested that workers who were never exposed to arsenic-in-air levels in excess of 500 $\mu g/m^3$ (0.5 mg) did not show a statistically significant increase in

respiratory cancer. Careful assessment of the Higgins study demonstrates that in the low exposure categories the statistical sensitivity was low for the detection of respiratory cancer. This study suggests a threshold value but the evidence is not conclusive and not supported by the other studies.

A second series of papers was written analyzing the mortality status of workers at the ASARCO Copper Smelter in Tacoma, Washington. The exposure in this smelter is also to inorganic trivalent arsenic compounds.

Pinto, Enterline and Henderson (1977) examined the mortality experience for the period 1949-1973 of a group of retirees who had been employed in the ASARCO Smelter at Tacoma. They concluded that there was an excess risk of death due to respiratory cancer and that this excess risk was related to both intensity and duration of exposure to inorganic trivalent arsenic although total arsenic exposure would seem to be a better predictor of respiratory cancer than duration of exposure.

Enterline and Marsh (1982) conducted a study of the mortality experience of 2802 men who worked one year or more at the ASARCO smelter during the period 1940-1964. The mortality experience of this cohort was established between 1941 and 1976. Cancer mortality

among this group was significantly elevated due mainly to cancer of the respiratory system. It was their opinion as a result of this study that the excess risk of respiratory cancer was due to exposure to inorganic arsenic in the workplace and that there was a dose-response relationship between increased risk of respiratory cancer and occupational exposure to inorganic trivalent arsenic compounds.

A study of decedents previously employed by the Dow Chemical Company was carried out by Ott, Holder and Gordon (1974) on the basis of their exposure to inorganic arsenic compounds, 95% of which were reported to be pentavalent. It was the opinion of the authors that there was a three-fold increase in death due to respiratory cancer among those exposed to these inorganic pentavalent arsenic compounds as compared with those who were not exposed to arsenicals. It was the conclusion of Blejerand Wagner that if there was a no-effect level, it would be in the very low (less than 3μg As/m^3 air) level.

A mortality study was carried out by Mabuchi, Lillienfeld and Snell (1979). They examined the vital status of 1393 workers exposed chiefly to inorganic trivalent arsenic compounds at the Allied Chemical plant. They concluded on the basis of their study that there was a statistically significant increase in

respiratory cancer, that there was a causal relationship between this excess risk of respiratory cancer and occupational exposure to inorganic trivalent arsenicals and that a dose-response effect could be demonstrated.

Conclusion and Recommendation

The epidemiological evidence supports the conclusion that there is an increased risk of respiratory cancer as a result of exposure to inorganic arsenic compounds both pentavalent and trivalent, and that a dose-response gradient of increasing lung cancer risk with increasing exposure has been observed in the various studies. This dose-response relationship has not been demonstrated between sulfur dioxide or any of the other non-arsenical exposures which have been investigated in these workplaces.

Although there has been a suggestion that a threshold for carcinogenicity exists for inorganic arsenic compounds, there are serious doubts about this, and further investigation is to be carried out by Welch and Higgins.

It is reasonable at this time to accept the more broadly supported no-threshold position with respect to these compounds. The ideal exposure to inorganic compounds of arsenic on this basis would be zero.

Arsenic is a natural occurring element. It is ubiquitous in the environment. A zero level of exposure is not feasible.

The Risk Assessment portion of this document states that the ICRP (ICRP 1977:para 96) has found that the level of occupational mortality in a "safe" industry is less than 10^{-4} cases per year (1 case per 10,000 workers per year). On the basis of the calculations shown in that section, a 45 year working lifetime exposure to 100 µg As/m^3 air would result in 20 excess deaths per 10,000 workers per year from respiratory cancer; a 45 year working lifetime exposure to 50 µg As/m^3 air would result in 10 excess deaths per 10,000 workers per year, and a 45 year working lifetime exposure to 10 µg As/m^3 air would result in 2 excess deaths per 10,000 workers per year. If the time-weighted average exposure to arsenic and arsenic in inorganic compounds was set at 10 µg/m^3 air this would result in the total amount of risk from all hazards in the workplace being comparable to the risks observed in occupations which are at the lower end of the range of risks observed in various occupations.

In the Province of Ontario the time-weighted average exposure limit for arsenic and its inorganic compounds is 0.05 mg/m^3. From the evidence available at this time, it is recommended that the time-weighted

average exposure limit for arsenic and its inorganic compounds be reduced to 0.01 mg (10 μg)/m^3 of air.

JOH:fn

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TABLE I

NORMAL VALUES FOR
NON-OCCUPATIONALLY EXPOSED PERSONS

Tissue	Arsenic	
	ppm	µmol/L
blood	0.1 - 0.5	-
urine	0.01 - 0.3	0.1335 - 4.0053
hair	0.5 - 2.0	-
nails	0.5 - 5.5	-

(adapted from U.S. DHEW 1976)

ppm = mg/L = mg/kg

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nails	0.5 - 5.5	-

(adapted from U.S. DHEW 1976)

ppm = mg/L = mg/kg

TABLE II

NUMBER OF DEATHS, DEATHS DUE TO CANCER, DEATHS DUE TO CANCER BY SITE

	Sheep Dip Powder Factory Workers			All Other Groups		
	# Deaths	% Deaths	% Cancer Deaths by Site	# Deaths	%Deaths	% Cancer Deaths by Site
All Causes	75	100		1216	100	
All Cancers	22	29.3	100	157	12.9	100
Cancer Respiratory Organs	7		31.8	25		15.9
Cancer Skin	3		13.6	2		1.3
Buccal Cavity & Pharynx	2		9.1	10		6.4
Digestive Organs & Peritoneum	5		22.7	91		58.0
Genito-urinary Organs	2		9.1	13		8.3
Other Sites or specified	3		13.6	16		10.2

(adapted from Hill and Faning, 1948)

TABLE III

PROPORTION OF CANCER DEATHS IN THE FACTORY POPULATION DISTINGUISHING TYPE OF WORK

Description of Work (By Factory Definition)	Cancer	All Other Causes of Death	Total	Due to Cancer
Chemical Workers	16	25	41	39.0
Engineers and Packers	3	7	10	30.0
Others (builders, printers, watchmen, carters, box-makers, sundries)	3	21	24	12.5
	22	53	75	29.3

(adapted from Hill and Faning, 1948)

TABLE IV

RELATIVE RISKS FOR SELECTED CAUSES OF DEATH (1964-1977) BY TOTAL YEARS OF EMPLOYMENT PRIOR TO 1964 IN THE SMELTER AND IN AREAS WITH HEAVY OR MEDIUM EXPOSURE TO ARSENIC

Cause	Years at Heavy/Medium Arsenic Exposure	Years of Employment 0-9	10-14	15 - 24	25	Total*
All causes	>4	1.14	1.32	1.33	1.07	1.14
	0-4	1.14	0.98	1.09	1.03	1.06
	0	1.00	0.86	1.13	1.10	1.00
Respiratory cancer‡	>4	2.09	2.41	1.85	3.53	1.95
	0-4	1.13	1.20	0.74	3.60	1.30
	0	1.00	0.93	0.87	1.92	1.00
Circulatory disease	>4	0.73	1.13	1.39	0.88	0.94
	0-4	1.05	1.01	1.14	0.80	0.96
	0	1.00	0.72	1.28	1.13	1.00
Respiratory diseases§	>4	1.34	2.08	0.64	1.55	1.50
	0-4	0.98	0.27	0.97	0.87	0.91
	0	1.00	1.09	0.82	0.87	1.00
Ill-defined conditions, senility†	>4	0.59	1.64	0.51	0.65	0.59
	0-4	1.39	3.86	1.20	1.65	1.39
	0	1.00	2.78	0.87	1.11	1.00
External causes	>4	1.20	0.43	1.60	0.46	1.07
	0-4	1.30	0.56	1.13	1.27	1.17
	0	1.00	0.98	1.27	0.55	1.00

* Controlling for length of employment

† Based on main effects model

‡ Test of linear trend within employment groups with years at heavy or medium exposure, $p<0.01$

§ Test of linear trend within employment groups with years at heavy or medium exposure, $p = 0.19$

(Lubin et al 1981)

TABLE V

Observed and Expected Deaths for Respiratory Cancer with Standardized Mortality Ratios (SMR's), by Length of Employment Group, 1938-77

Length of Employment Group	Respiratory Cancer Deaths		
	Observed	Expected	SMR
1 (25+ yrs)	127	31.14	408[a]
2 (15-24 yrs)	44	17.00	259[a]
3 (10-14 yrs)	25	10.77	232[a]
4 (5-9 yrs)	29	12.73	228[a]
5 (1-4 yrs)	77	34.16	225[a]

[a] Significant at 1% level.

(From Lee and Fraumeni (1969))

TABLE 11

Cause-Specific Mortality for 1800 Smelter Workers from 1938 to 1978 by Sample Stratum

Cause of Death	ICD Code (8th Rev)	Heavy Obs	Heavy Exp*	Heavy SMR	Other Obs	Other Exp†	Other SMR
All causes		167	103.0	162‡	649	512.6	127‡
Tuberculosis	010-019	1	1.7	60	7	6.4	109
All malignancies	140-209	37	16.3	227‡	125	79.1	158‡
Digestive	150-159	5	5.5	90	25	26.8	93
Respiratory	160-163	24	4.6	527‡	56	20.9	267‡
Urinary	188-189	2	1.0	195	10	5.1	197§
Other		6	5.2	115	34	26.3	129
Diseases of heart	390-429	65	40.6	153‡	241	195.5	123‡
Ischemic heart disease	410-413	53	30.0	177‡	199	145.5	137‡
Vascular lesions of CNS	430-438	6	6.9	87	55	37.1	148‡
Influenza and pneumonia	470-474, 480-486	5	2.8	178	17	14.4	118
Cirrhosis of the liver	571	3	1.6	189	15	7.6	197‡
All accidents	800-949	13	9.3	140	43	51.1	84
Motor vehicle	810-823	4	3.5	114	15	20.6	73
Suicide	950-959	3	2.8	106	17	13.8	123
Homicide	960-978	0	.5	-	1	2.6	39
All other causes	Residual	34	21.1	161‡	128	104.9	122§
All respiratory diseases‖	460-519	16	6.2	257‡	56	32.9	170‡

* Expected deaths based on 6,843 person-years of experience for 277 men.

† Expected deaths based on 37,478 person-years of experience for 1,523 men.

‡ Significant at .01 level.

§ Significant at .05 level.

‖ Standard population for comparison was U.S. white males for this cause of death only.

(From Welch, Higgins et al 1982)

TABLE VII

Mortality for 1800 Smelter Workers from 1938 to 1978
by TWA and Ceiling Arsenic Categories
Defined as of Entry into Cohort

Arsenic Category ($\mu g/m^3$)	N	Person-Years	All Causes Obs	All Causes Exp	All Causes SMR	Respiratory Cancer Obs	Respiratory Cancer Exp	Respiratory Cancer SMR	Ischemic Heart Disease Obs	Ischemic Heart Disease Exp	Ischemic Heart Disease SMR	All Respiratory Diseases* Obs	All Respiratory Diseases* Exp	All Respiratory Diseases* SMR
TWA														
<100	547	13152	219	196.7	111+	11	7.9	138	72	56.9	126+	24	13.1	183‡
100	542	14157	216	178.0	121‡	22	7.3	303‡	67	49.6	135‡	18	11.6	156
500	565	13460	292	184.7	158‡	29	7.7	375‡	88	52.1	169‡	21	10.9	193‡
>5000	146	3552	89	56.1	159‡	18	2.6	704‡	25	16.9	148+	9	3.5	256‡
Ceiling														
Low (<100)	445	10591	165	152.1	108	8	6.2	129	48	44.4	108	18	9.2	196‡
Medium (100-499)	276	7083	80	80.5	99	4	3.4	116	28	22.3	126	5	6.0	83
High (500-4999)	833	20757	416	288.5	144‡	41	11.8	348	129	81.3	159‡	36	18.1	199‡
Very High (>5000)	246	5889	155	94.4	164‡	27	4.1	662‡	47	27.5	171‡	13	5.8	223‡

* SMRs for all respiratory diseases were derived using U.S. white males as the standard population; all other causes of death used Montana white males as the standard.

\+ Significant at .05 level.

‡ Significant at .01 level.

(From Welch Higgins et al (1982))

TABLE VIII

S M R 's for 1800 Copper Smelter Workers by Arsenic TWA and Ceiling as Defined at Entrance into Cohort, Follow-up from 1938 to 1978

TWA ($\mu g/m^3$)	Ceiling Category: Low Obs	Low Exp	Low SMR	Medium Obs	Medium Exp	Medium SMR	High Obs	High Exp	High SMR	Very High Obs	Very High Exp	Very High SMR	Total Obs	Total Exp	Total SMR
<100	7	6.1	115	1	0.89	113	3	0.97	310	0	0	-	11	7.9	138
100-500	1*	0.13	765	3	2.5	120	18	4.5	398†	0	0.1	-	22	7.3	303†
							20	6.3	318†	9	1.4	641†	29	7.7	375†
≥5000										18	2.6	704†	18	2.6	704†
Total	8	6.2	129	4	3.4	116	41	11.8	348†	27	4.1	662†			

* This man had a low ceiling arsenic exposure, but TWA was medium (177 $\mu g/m^3$) due to 20 days spent in high areas, which was sufficient to increase his TWA, but not of great enough duration to place him in a higher ceiling category.

† Significant at 0.01 level.

(From Welch, Higgins et al 1982)

TABLE IX

Mortality for Respiratory Cancer 1938 to 1978 by Cumulative Exposure to Arsenic and Time Worked for 1800 Men Working at the Anaconda Copper Smelter

Time Worked (yr)	Cumulative Arsenic Exposure ug/m^3) . Years											
	< 500			500 - 2000			2000-12000			12000+		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
<10	4	4.4	90	7	3.3	209*	10	2.1	476†	6	1.0	629†
10-	0	0.5	-	1	1.3	80	9	2.1	431†	6	1.1	559†
20-	0	0.3	-	0	0.6	-	3	1.4	210	12	2.0	600†
30+	0	0.5	-	1	0.6	181	5	1.1	439†	16	3.2	493†
Total‡	4	5.8	69	9	5.7	157	27	6.8	400†	40	7.3	550†

* Significant at .05 level.

† Significant at .01 level.

‡ Totals of expected numbers of deaths do not agree with sums of individual latency categories due to rounding of calculations of person-years.

(Welch, Higgins et al 1982)

TABLE X

OBSERVED AND EXPECTED DEATHS AND STANDARDIZED MORTALITY RATIOS FOR SELECTED CAUSES OF DEATH OF 527 MALES OF COHORT UNDER STUDY*

Cause of Death	Disease Classification†	Observed	Expected	SMR
All Causes		324	288.7	112.2‡
Cancer	140-205	69	46.5	148.4‡
Digestive	150-159	20	16.4	122.0
Respiratory	160-164	32	10.5	304.8‡
Lymph, etc.	200-203, 205	2	2.1	95.2
Urinary	180, 181	3	3.3	90.9
All Other Cancers		12	14.2	84.5
Stroke	330-334	43	38.0	113.2
Heart Disease	400-443	144	132.3	108.8
Coronary Heart Disease	420	120	110.2	108.9
All Other Heart Disease		24	22.1	108.6
Respiratory Disease	480-493, 500-502	11	10.8	101.8
All Other Causes		57	61.8	92.2

* Cohort consisted of living male pensioners from a copper-smelting plant who were living January 1, 1949, and whose causes of death were noted through December 31, 1973.

† Numbers from rubrics of 7th Revision of International Classification of Diseases.[10]

‡ $P<.05$

(adapted from Pinto, Henderson and Enterline, 1978)

TABLE XI

Observed and Expected Respiratory Cancer Deaths and SMR by Arsenic Exposure Index

Exposure Index (Mean Index)	No. of Men	Respiratory Cancer Deaths		
		Observed	Expected	SMR
<2000 (1514)	36	1	0.9	111.1
2000-2999 (2513)	109	4	2.1	190.5
3000-5999 (4317)	205	11	3.9	282.0[a]
6000-8999 (7473)	109	7	2.3	304.3[a]
9000-11,999 (10,135)	38	4	0.7	571.4[a]
>12,000 (14,712)	29	5	0.6	833.3[a]

[a] $p<0.05$

(From Pinto, Enterline, Henderson & Varner 1977)

TABLE XII

Observed and Expected Respiratory Cancer Deaths and Standardized Mortality Ratios by Intensity and Duration of Exposure

Intensity of Exposure µg/L Urine	Duration of Exposure					
	<25 Yr			≥25 Yr		
	Obs	Exp	SMR	Obs	Exp	SMR
50-199	2	2.1	95.2	10	3.6	277.8[a]
200-349	4	1.5	266.7	8	2.2	363.6[a]
≥350	3	0.5	600.0[a]	5	0.6	833.3[a]

[a] $p<0.05$

(Adapted from Pinto, Enterline, Henderson & Varner 1977)

TABLE XIII

Cancer Mortality 1941-1976 among 2802 Workers Who Worked a Year or More during 1940-1964, by Type of Cancer: Tacoma, Washington Copper Smelter Workers

Type of Cancer	Observed Deaths	SMR†‡	SMR§
All cancer	231	123.6**	129.9**
Buccal cavity and pharynx	7	110.7	142.9
Digestive organs	65	108.9	117.4
Respiratory system	104	189.4**	198.1**
Prostate	11	79.0	75.8
Kidney	6	133.3	131.6
Lymphatic & Hematopoietic tissue	17	93.8	92.4
All other	21	71.3	76.1

(From Enterline and Marsh 1982)

** $p<0.01$

† SMR = standardized mortality ratio.

‡ Expected deaths based on US white males.

§ Expected deaths based on Washington State white males.

TABLE XIV

Respiratory Cancer Deaths and Standardized Mortality Ratios (SMR's) by Cumulative Arsenic Exposure Lagged 0 Years and 10 Years: Tacoma, Washington, Copper Smelter Workers

Cumulative Exposure (µg/As/L) (urine-years)		0-Years Lag			10-Years Lag		
		Observed Deaths	Expected† Deaths	SMR	Observed Deaths	Expected† Deaths	SMR
<500	(302)‡	8	3.96	202.0	10	6.44	155.4
500-1500	(866)	18	11.36	158.4	22	12.45	176.6*
1500-3000	(2173)	21	10.33	203.2**	25	11.49	226.4*
3000-7000	(4543)	26	14.12	184.1**	22	12.39	177.6*
7000+	(13457)	31	12.74	243.4**	24	9.75	245.2*

* $p<0.05$
** $p<0.01$
\+ Based on Washington State white males.
‡ Estimated mean of class interval.

(Taken from Enterline and Marsh, 1982)

TABLE XV

Respiratory Cancer Deaths and Standardized Mortality Ratios (SMR's) by Duration and Intensity of Exposure: Tacoma, Washington, Copper Smelter Workers

Duration of Exposure (years)	Intensity Estimate: Low† No. at Risk	Observed Deaths	Expected§ Deaths	SMR	High‡ No. at Risk	Observed Deaths	Expected§ Deaths	SMR
<10	687	15	8.83	169.9	824	25	12.26	203.9**
10-19	149	7	2.61	268.2*	168	11	3.42	321.6**
20-29	225	10	3.59	278.6**	171	16	2.77	577.6**
30+	159	9	2.98	302.0**	165	11	3.17	347.0**
Total	1220	41	18.01	227.7**	1328	63	21.62	291.4**

* $p<0.05$

** $p<0.01$

† low = <290 µg/As/L urine (mean 163)

‡ high =>290 µg/As/L urine (mean 477)

§ Based on Washington State white males

(Enterline and Marsh 1982)

TABLE XVI

ESTIMATED ARSENIC LEVELS BY JOB CATEGORY

Job Category	8 Hr TWA Concentration of Arsenic mg/cu m
Group 1	5.0
Group 2	3.0
Group 3 (jobs associated with arsenical production out of the area of high dust exposure)	1.0
Group 4 (jobs involving either the formulation of nonarsenicals within the production unit or requiring only intermittent time in the areas of high exposure)	0.1

(taken from Ott, Holder and Gordon, 1974)

TABLE XVII

OBSERVED AND EXPECTED DEATHS DUE TO RESPIRATORY CANCER BY EXPOSURE CATEGORY

Exposure Levels: TWA Concentration X Months of Exposure	Average Log_e (Dosage) mg	No. of Total Deaths (N=173*)	Respiratory Cancer Deaths: Observed (N = 28)	Observed / Expected	Expected
<1	3.74	26	1	1.77	0.6
1-1.9	4.64	17	2	1.01	2.0
2-3.9	5.53	24	4	1.38	2.9
4-5.9	6.04	22	3	1.36	2.2
6-11.9	6.68	27	3	1.70	1.8
12-23.9	7.35	18	2	0.97	2.1
24-59.9	8.17	13	3	0.77	3.9
60-95.9	8.78	13	5	0.79	6.3
96 +	10.30	13	5	0.72	7.0

* 138 worked in the exposure area less than 1 year; 16 of these died of respiratory cancer.
+ After Ott et al, 1974, Arch. Env. Health 29:250

(taken from Blejer and Wagner, 1976)

TABLE XVIII

RATIO OF OBSERVED TO EXPECTED RESPIRATORY CANCER DEATHS BY 40-YEAR DOSAGE AND DAILY EXPOSURE CATEGORIES

Projected Exposure Levels		
40-Year Dosage Loge mg	Daily TWA Dose mg/m^3	Respiratory Cancer Deaths Observed/ Expected
3.74	1	0.6
4.84	3	2.0
5.53	6	2.3
6.04	10	2.2
6.68	20	1.8
7.35	40	2.1
8.17	90	3.9
8.78	160	6.3
10.30	740	7.0

* Modified from Ott et al, 1974, Arch. Environ. Health 29:250

(taken from Blejer and Wagner, 1976)

TABLE XIX

Observed and Expected Numbers of Deaths and SMR's from Lung Cancer by Various Employment Characteristics among Males

Employment Characteristics	Number of Persons	Number of Person-Years	Lung Cancer Observed (O)	Lung Cancer Expected (E)	Lung Cancer SMR	All Other Causes Observed (O)	All Other Causes Expected (E)	All Other Causes SMR
Work Exposure Group								
Arsenical production	205	4,456.3	1	2.6	.38	42	35.0	1.20
Predominantly arsenical production	259	4,898.8	12	3.6	3.36*	49	50.3	.97
Predominantly nonarsenical production	110	2,405.2	0	1.7	.00	19	25.7	.74
Unspecified production	130	878.1	2	.3	6.72	3	5.7	.53
Maintenance/Shipping	266	5,553.6	8	5.1	1.56	60	68.4	.88
Office	77	1,054.8	0	.4	.00	1	5.5	.18
Year First Employed								
Before 1946	78	1,745.6	10	2.5	3.96*	27	28.7	.96
1946-1954	473	11,414.9	13	8.8	1.48	110	116.8	.94
1955-1964	280	4,545.6	0	2.1	.00	23	29.4	.78
After 1964	216	1,539.6	0	.3	.00	4	5.6	.71
Duration of Employment								
Less than 4 months	482	9,024.7	4	5.4	.74	71	74.1	.96
4-11 months	264	4,676.4	6	3.4	1.75	41	45.7	.90
1-4 years	159	2,720.0	1	1.9	.52	25	26.1	.96
5-24 years	108	2,058.2	3	1.6	1.87	22	22.9	.96
25 or more years	35	767.5	9	1.3	6.79*	15	21.7	.69

NOTE: SMR = O/E Ratio
*p≤.05

(Mabuchi, [illegible]enfeld and Snell, 1979)

TABLE XX

Respiratory Cancer Deaths and Standardized Mortality Ratios (SMR's) by Cumulative Arsenic Exposure (Adapted from Table 8, Enterline and Marsh (1982))

Cumulative Exposure (μg As-yr/L Urine)		Observed Lung Cancer Deaths	Expected Lung Cancer Deaths[2]	SMR
0-500	(302)[1]	8	3.96	202.0
500-1000	(866)	18	11.36	158.4
1500-3000	(2173)	21	10.33	203.2
3000-7000	(4534)	26	14.12	184.1
7000+	(13457)	31	12.74	243.4

NOTE: 1. Estimated mean of class interval.

2. Based on Washington State white males.

Maximum Likelihood Parameter Estimates

$$O = (A + 1) E + B \times I \times E$$

where O = number of observed lung cancer deaths (μg As . yr/L)

A = estimated relative increase in expected number of lung cancer deaths

E = expected number of lung cancer deaths

B = estimated relative increase in the lung cancer risk (relative to the "expected" number of cases) per unit increase in the arsenic exposure index.

I = Arsenic exposure index (μg As x yr/L urine)

Parameter	Estimate	Asymptotic Estimate of Standard Error
Intercept (A)	0.63	0.11
Slope (B)	5.9×10^{-5}	1.3×10^{-5}

TABLE XXI

CALCULATION OF MORTALITY DUE TO ARSENIC EXPOSURE AND ACCIDENTS IN THE WORKPLACE

Age Group	Life Years In Age Group[1,2] (Col.A)	Average Life Years Remaining[1] (Col. B)	Lung Cancers Per Year Per 100,000[1] (Col. C)	Cumulative Arsenic Exposure[3] ($\mu g\ As\text{-}yr/m^3$) (Col. D)	Lung Cancer Cases Due To Arsenic Exposure[4] (Col. E)	Life Years Lost by Arsenic Induced Cancer (Col. F)	Accidental Deaths[5] (Col. G)	Life years Lost by Accidental Deaths (Col. H)
20 - 24	498096	50.4	0.18	25	0.007	0.3	92.7	4674.1
25 - 29	494608	45.7	0.28	75	0.03	1.4	92.1	4208.5
30 - 34	491529	41.0	1.24	125	0.23	9.4	91.5	3752.2
35 - 39	487686	36.3	2.97	175	0.76	27.6	90.8	3296.1
40 - 44	481815	31.7	12.32	225	4.01	127.0	89.7	2843.7
45 - 49	471933	27.2	34.73	275	13.52	367.8	87.9	2390.3
50 - 54	455635	23.1	71.62	325	31.82	735.0	84.8	1959.7
55 - 59	430320	19.2	135.75	375	65.72	1261.	80.1	1538.3
65 - 69	341968	12.5	331.58	450	153.08	1913.5	73.2	1149.6
70 - 74	275559	9.8	435.26	450	161.19	1586.8	0	0
75 - 79	198825	7.5	929.7	450	128.70	965.2	0	0
80 - 84	121324	5.5	486.46	450	79.68	438.2	0	0
85 +	77409	2.3	318.53	450	33.87	76.6	0	0
TOTAL	5219992				782.90	9241.9	782.8	25812.2

Average lung cancer rate attributable to arsenic exposure = 782.90/5219992 = 1.5×10^{-4}/year (1.5 cases per year per 10,000 workers).
Average life expectancy lost per arsenic induced lung cancer = 9241.9/782.9 = 11.8 years.
Average life-expectancy lost per accidental fatality in the workplace = 33 years.

Notes:

(1) Based on Ontario males for the years 1975-77. Size of population at age 20 is 100,000.
(2) Unadjusted for mortality due to arsenic exposure or accidental fatalities in the workplace.
(3) Arsenic exposure level is taken to be 10 $\mu g/m^3$.
(4) Risk factor is taken to be 3×10^{-4}/μgAs-yr/L "expected" lung cancer. "Expected" lung cancers were calculated on the basis of Ontario male population data.
(5) Accidental fatality rate is taken to be 1.86×10^{-4} per year between age 20 and 65. (1.86 deaths per year per 10,000 workers).

Formulae

Col E = Col A x Col C x 10^{-5} x Col D x 3 x 10^{-4}
Col F = Col E x Col B
Col G = Col A x 1.86 x 10^{-4}
Col H = Col G x Col B

TABLE XXII

Number of Lung Cancer Cases Attributable to Continual Exposure to 10 ug As/m^3 per 10,000 Workers Per Year Calculated Using Various Urine to Air Conversion Factors, Risk-Exposure Functions, and Study Populations

Study Population	Risk-Exposure Function		Ratio of Arsenic in Urine (µg/L) to Arsenic in Air (ug/m^3)(1)			
	Intercept (A)	Slope (B)	0.3	1.0	1.5	3.3
Retirees	0.0	1.6×10^{-4}	0.2	0.8	1.2	2.6
Retirees	-0.9	3.0×10^{-4}	0.5	1.5	2.3	5.0
Total Population (0 year lag)	0.0	1.1×10^{-4}	0.2	0.6	0.8	1.8
Total Population (0 year lag)	0.63	5.9×10^{-4}	0.09	0.3	0.4	1.0

Note: (1) Pinto, Enterline, Henderson and Varner (1977) found the ratio of arsenic in urine (ug/L) to arsenic in air (ug/m^3) to be 3.3. The estimates obtained from the mathematical model (see footnote) gave a range from 0.3 to 1.5 for the various aerodynamic diameters considered.

TABLE XXIII

ACCIDENTAL FATALITY RATES IN VARIOUS OCCUPATIONS
(Adapted from ICRP 1977a)

Accidental Fatalities per 10,000 worker per year

Occupation	1969	1972
Trade	0.72	0.72
Manufacturing	0.93	0.96
Service	1.20	1.20
Government	1.32	1.32
Transport	3.78	3.62
Agriculture	6.50	6.57
Construction	7.36	7.10
Mining	11.67	10.00

TABLE XXIV

ACCIDENTAL FATALITY RATES IN VARIOUS OCCUPATIONS
IN ONTARIO 1978-198L
(Adapted from ACOHOS 1983)

Industry	Accidental Fatalities per 10,000 workers per year (1) 1978	1979	1980	1981
Agriculture	2.0	1.4	1.6	3.0
Forestry	9.0	5.4	12.2	8.0
Mining, Quarrying and Oil Wells	6.4	4.8	14.8	5.2
Manufacturing	0.6	0.6	0.60	0.4
Constuction	2.8	3.6	3.8	3.4
Transportation Communications and Utilities	3.4	4.2	4.2	4.0
Trade	0.2	0.4	0.2	0.2
Community Business and Personal Service	0.2	0.2	0.2	0.2
Public Administration	2.8	2.0	1.4	2.4
Other (Fishing)[2]	0	18.0	0	0

Note 1. The data were given originally in terms of fatalities per million man-hours worked. In order to convert to a fatality rate in terms of man-years, the conversion, 1 man-year = 2000 man-hours (i.e. 40 hrs/week x 50 weeks/year), was used.

2. Based on small populations.

TABLE XXV

ARSENIC BALANCE IN REFERENCE MAN

Intake	
Food and Fluids	1000 µg/day
Airborne	1.4 µg/day
Losses	
Urine	50 µg/day
Feces	800 µg/day
Hair and Nails	0.5 µg/day
Other Losses	150 µg/day

TABLE XXVI

AIR TO BLOOD FRACTION IN MAN FOR ARSENIC

Tidal Volume 750 cm^3
Fraction Absorbed from GI Tract to Blood 0.05

Aerodynamic Diameter	Fraction Lung to Blood (A)	Fraction Lung to G.I. Tract (B)	G.I. Tract to Blood (C)	Air to Blood (A + C)
0.01	0.2547	0.5583	0.0279	0.2826
0.06	0.151	0.502	0.0251	0.1761
0.20	0.0697	0.2383	0.0119	0.0816
0.60	0.0508	0.1732	0.0087	0.0595
1.0	0.0671	0.2459	0.0123	0.0794
2.0	0.1353	0.6677	0.0334	0.1687
3.0	0.1523	0.7787	0.0389	0.1912
4.0	0.1550	0.8210	0.0411	0.1961
6.0	0.1460	0.8470	0.0424	0.1884
10.0	0.1031	0.8979	0.0449	0.1480

See Table XIV for the calculation of "Fraction Lung to Blood" and "Fraction Lung to G.I. Tract".

Air to Blood Fraction = A + C

Fraction G.I. Tract to Blood = 0.05 x B

TABLE XXVII

CALCULATION OF LUNG TO BLOOD AND LUNG TO GI TRACT DISTRIBUTION OF INHALED ARSENIC

Deposited Fraction of Inhaled Particles

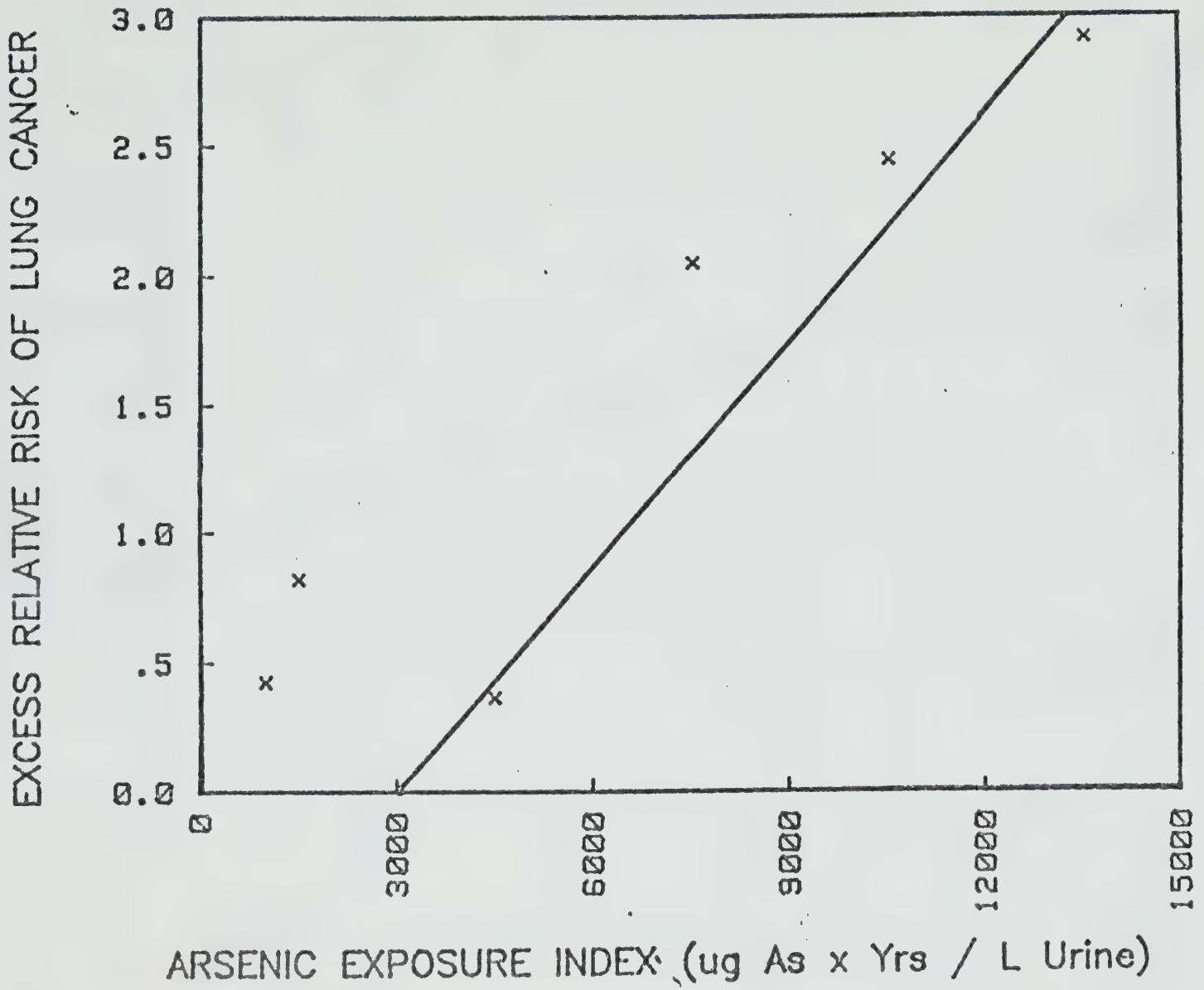
Aerodynamic Diameter (Micron)	Nasopharynx (A)	Trachea Bronchus (B)	Pulmonary (C)	Fraction to Blood from Lung	Fraction to GI Tract from 'Lung'
0.01	0	0.307	0.506	0.2547	0.5583
0.06	0	0.068	0.585	0.151	0.502
0.20	0	0.027	0.281	0.0697	0.2383
0.60	0	0.020	0.204	0.0508	0.1732
1.0	0.036	0.027	0.250	0.0671	0.2459
2.0	0.406	0.051	0.346	0.1353	0.6677
3.0	0.552	0.071	0.308	0.1523	0.7787
4.0	0.654	0.084	0.238	0.1550	0.8210
6.0	0.799	0.091	0.103	0.1460	0.8470
10.0	0.992	0.007	0.002	0.1031	0.8979

Fraction to Blood From "Lung" = $0.1 \times A + 0.5 \times B + 0.2 \times C$

Fraction to GI Tract from "Lung" = $0.9 \times A + 0.5 \times B + 0.8 \times C$

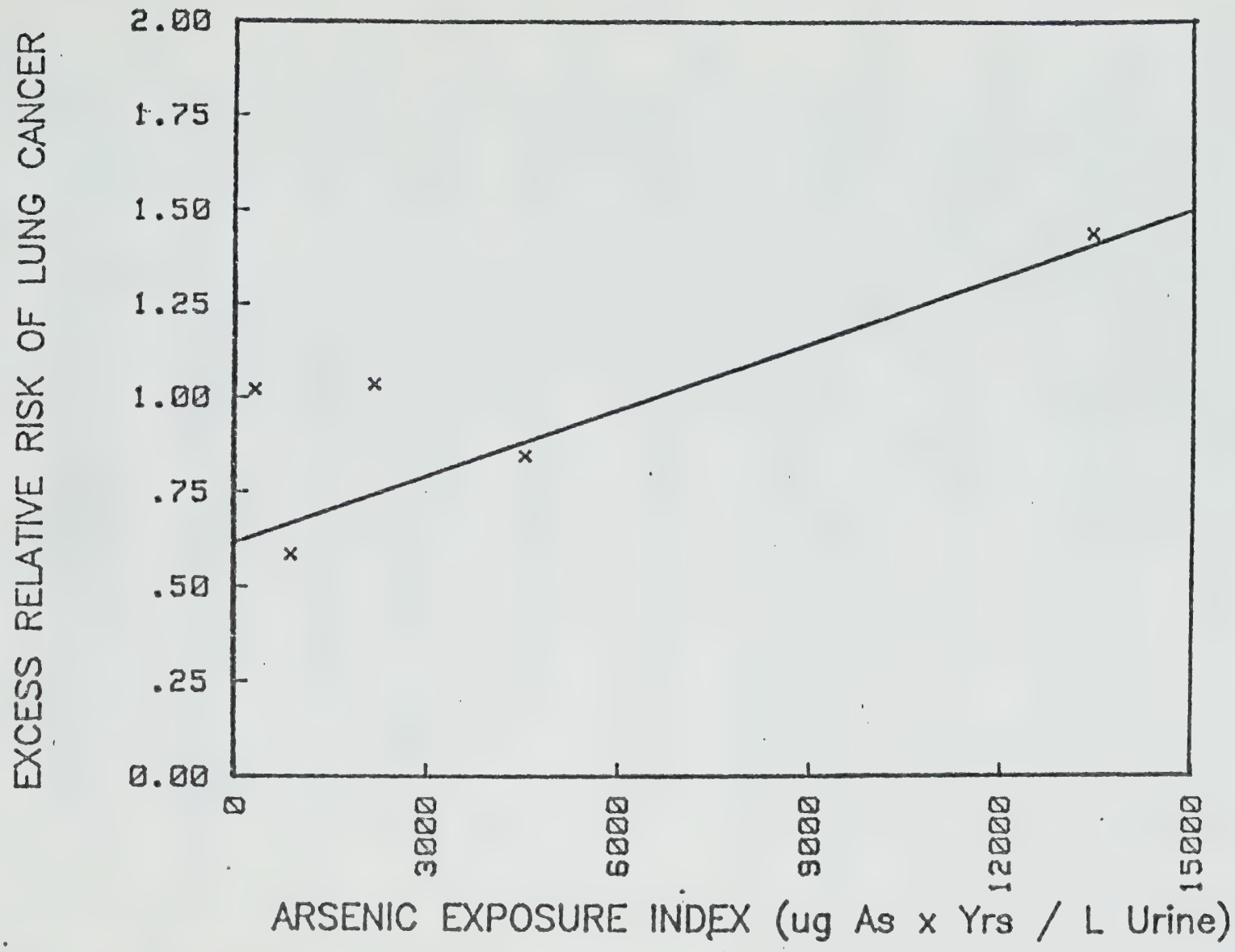
Data Source: Bates, Fish, Hatch, Mercer, Marrow Heath Physics 12, 193-207, (1966), and
IRCP Committee 2 (Publication 19)

FIG 1: LUNG CANCER RISK AND ARSENIC EXPOSURE IN RETIREES



SOURCE: ENTERLINE & MARSH (1982)

FIG 2: LUNG CANCER RISK & ARSENIC EXPOSURE IN TOTAL POPULATION



SOURCE: ENTERLINE & MARSH (1982)

An analysis of health effects of arsenic and its inorganic compounds & recommendations for an occupational Standard 94

BIBLIOGRAPHY

ACOHOS, 1983, 5th Annual Report, Advisory Council and Occupational Safety, Vol. 1, Ontario Ministry of Labour.

American Conference of Governmental Industrial Hygienists Inc. ACGIH 1980 Documentation of the Threshold Limit Values Fourth Edition.

Axelson, O., 1980. Arsenic Compounds and Cancer. J. Tox. and Env. Health, V.6, #5 and #6, Sept. -Nov. 1980, pp. 1229-1235.

Beckman, G.L., Beckman, I., Nordenson, 1977. Chromosome Aberrations in Workers Exposed to Arsenic National Institute of Environmental Health Perspectives, Vol. 19, Research Triangle Park, No. Carolina, U.S. DHEW Public Health Service, Nat. Inst. Health, Pub. No. (NIH) 77-218.

Bates, Fish, et al. 1966. Retention Models for Internal Dosimetry of the Human Respiratory Tract. Health Physics, 12, 1.

Beaudoin, Allan, R-1974. Teratogenicity of Sodium Arsenite in Rats, Teratology, 10: 153-158.

Benko, V. and Symon, K., 1970. The cumulative dynamics of some tissues of hairless mice inhaling arsenic. Atmos. Environ., 4:157-161.

Blot, W.J. and Fraumeni, J.F., 1955. Arsenical Pollution and Lung Cancer, Lancet, Vol. 2, July 26, 1975, pp. 142-44.

Blejer, H.P. and Wagner, W., 1976. Case Study 4. Inorganic Arsenic. Ambient Level Approach to the Content of Occupational Cancerigenic Exposure. Ann. New York Acad. Sci. 271: 179-186.

Bowen, H.J.M., 1975. Residence Times of Heavy Metals in the Environment. International Conference on Heavy Metals in the Environment, Toronto, Canada. Oct. 27 - 31. Proc. 1: 1-19.

Buchanan, W.C., 1962.
Toxicity of Arsenic Compounds.
Elsevier Pub. Co., Amsterdam.

Buchet, J.P., Lauwerys, R. and Roels, H., 1980.
Comparison of several methods for the determination of arsenic compounds in water and in urine.
Int. Arch. Occup. Environ. Hlth.,46: 11-29.

Buchet, J.P., Lauwerys, R. and Roels, H., 1981.
Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium metaarsenite by volunteers.
Int. Arch. Occup. Environ. Health (1981) 48: 111-118.

Carlsson, G., 1976.
Correlation between industrial arsenic exposure and excretion in urine. Examination report. Stockholm, The National Board of Industrial Safety, Department of Occupational Health.

Crecelius, E.A., 1976.
Changes in the chemical speciation of arsenic following ingestion by man. Presented at a conference of Arsenic in the Environment, October 5-8, 1976, Fort Lauderdale, Florida.

Enterline, P.E., 1974.
Respiratory Cancer Among Chromate Workers.
J. Occup. Med. 16: 523-26.

Enterline, P.E. and Gary M. Marsh, 1982.
Cancer Among Workers Exposed to Arsenic and Other Substances in a Copper Smelter.
American J. Epidemiology, Vol. 116: 6, 895-911.

Ferm, V.H., and Carpenter, S.J., 1968.
Malformation Induced by Sodium Arsenate.
J. Reprod. Fertility, Vol. 17, 199-201.

Ferm, V.H., R.E. Halmberg and N.H. Hanover, 1969.
Interrelationships of Selenium, Cadmium and Arsenic in Mammalian Teratogenesis.
Arch. Environ. Hlth., Vol. 18, June 1969.

Ferm, V.H., Saxon, A., and Smith, B.M., 1971.
The Teratogenic Profile of Sodium Arsenate in the Golden Hamster.
Arch. Environ. Hlth, 22: 557-560.

Fowler, B.A., Weissberg, J.G., 1974
Arsine poisoning
New England J. Med. 291 (1974) 1171-1174.

Frost, D.V., 1967. Arsenicals in biology - retrospect and prospect. Fed. Proc. Trace Elements in Nutrition 26(1): 194-208.

Gainer, J.H. and T.W. Pry, 1972.
Effects of Arsenicals on Viral Infections in Mice.
Amer. J. Vet. Res., 33: 2299-2307.

Goodman, A.G., Goodman, L.S. and Gilman, A. 1980
The Pharmacologic Basis of Therapeutics 6th edition
MacMillan Pub. Co. Inc., New York

Harrison, T.R. et al, 1958.
Principles of Internal Medicine.
34th Edition, Vol. 2, 764.

Health and Welfare Canada, 1975. Report of the Task Force on Arsenic in Ambient Air Environmenal Health Directorate, Health Protection Branch.

Hill, A. B., and Faning, E.L., 1948.
Studies in the Incidence of Cancer in a Factory Handling Inorganic Compounds of Arsenic. Mortality Experience in the Factory.
Br. J. Indust. Med. 5: 1-6.

Holland, R.H., McCall, M.S., and Lanz, H.C., 1959
A Study of Inhaled Arsenic - 74 in Man.
Cancer Research 19, 1154-56.

Hood, R.D., and Bishop, S.L., 1972.
Teratogenic Effects of Sodium Arsenate in Mice.
Arch. Environ. Hlth., 24, 64-65.

Holmquist, I., 1951.
Occupational Arsenical Dermatitis.
Acta Derm. Venereol. 31, (Suppl. 26) 1-214.

ICRP, 1975
International Commission on Radiological Protection
Report 23 of the Task Group on Reference Man.
Pergamon Press.

ICRP, 1977a
Recommendations of the International Commission on Radiological Protection.
Publication 6, Pergamon Press.

ICRP, 1977b Sowbro F.D. (editor)
Problems Involved in Developing an Index of Harm,
ICRP Publication 27, Pergamon Press, Oxford.

Jelinek, C.F., and R.E. Corneliussen, 1977.
Levels of Arsenic in the United States Food Supply.
Environmental Health Perspectives 19, 83-87.

Jones, H.B., and Grendon, A., 1975.
Environmental Factors in the Origin of Cancer and Estimation of the Possible Hazard to Man.
Food Cosmet. Toxicol. 18: 251-68.

Kyle, R.A., and Pease, G.L., 1965.
Hematologic Aspects of Arsenic Intoxication.
New England Journal of Medicine, Vol. 273, No. 1, p. 18.

Lee, A.M., and Fraumeni, Jr. J.F., 1969.
Arsenic and Respiratory Cancer in Man. An Occupational Study.
J. Natl. Cancer Inst. 42: 1045-52.

Lee-Feldstein, Anna 1981.
Arsenic and Respiratory Cancer Presented at the Arsenic Symposium.
Gaithersburg, MD., November 3-6, 1981.

Lubin, J.H., Pottern, L.M., Blot, Wm. J. et al, 1981.
Respiratory Cancer Among Copper Smelter Workers.
J. Occ. Med., V.23: 11, pp. 779-84.

Mabuchi, K., Lilienfeld, A.M., Snell, L.M., 1979.
Lung Cancer Among Pesticide Workers Exposed to Inorganic Arsenicals.
Archives of Env. Hlth., V. 34: 312-320.

Matonoski, F., Landau, E., and Elliot, E., May 1976.
Epidemiological Studies. Pilot Study of Cancer Mortality Near a Chemical Plant and Other Industries in Baltimore.
EPA Contract No. 68-01-2490, U.S.E.P.A., Washington.

Mealey, J. Brownell, G.L. and Sweet, W.H. 1959.
Radioarsenic in plasma, urine, normal tissues and intracranial neoplasms. Am. Med Assoc. Arch. Neurol. Psychiatry 81: 310-320.

Milham, S., and T. Strong, 1974.
Human Arsenic Exposure in Relation to a Copper Smelter, Environmental Research 7, 176-182.

Milham, Samuel, Jr., 1977.
Studies of morbidity near a copper smelter.
Environmental Health Perspectives, Vol. 19, pp. 131-132.

National Academy of Sciences, Washington, 1977.
Medical and Biological Effects of Environmental Pollutants: Arsenic.

National Institute for Occupational Safety and Health, (NIOSH) 1975.
Criteria for a Recommended Standard.....
Occupational Exposure to Inorganic Arsenic.
New Criteria - 1975. HEW (NIOSH).

National Research Council of Canada 1978. Effects of Arsenic in the Canadian Environment.

Nieben, B., 1968.
Arsine poisoning in a Metal Refining Plant - Fourteen Simultaneous Cases.
Acta Med. Scand. Suppl. 496, pp. 1-31

Oehme, F.W., 1972.
Mechanisms of Heavy Metal Toxicities.
Clin. Toxicol. 5 (2) 151-167.

Ott. M.G., Holder, B.B., and Gordon, H.L., 1974.
Respiratory Cancer and Occupational Exposure to Arsenicals.
Arch. Env. Hlth. 29: 250-255.

Peoples, S.A. 1964.
Arsenic Toxicity in Cattle.
Ann. N.Y. Acad. Sci. 111: 644-649.

Pershagen, G., Lind, B., Bjorklund, N.E. 1982.
Lung retention and toxicity of some inorganic arsenic compounds. In: Pershagen, G., Arsenic and lung cancer with specific reference to interacting factors: Thesis. Department of Environmental Hygiene, Karolinska Institute and the National Institute of Environmental Medicine, Stockholm.

Pinto, S.S., Henderson, V., Enterline, P.E., 1978.
Mortality Experience of Arsenic Exposed Workers.
Archives of Environmental Health, 33(6), 325-331.

Pinto, S.S., and Bennett, B.M., 1963
Effect of Arsenic Trioxide Exposure on Mortality.
Archives Environ. Hlth., Vol. 7.

Pinto, S.S., Enterline, P.E., Henderson, V., and Varner, M. 1977.
Mortality Experience in Relation to a Measured Arsenic Trioxide Exposure.
Environmental Health Persp., Vol. 19.

Pinto, S.S., Varner, M., Nelson, K.W., 1976.
Arsenic Trioxide Absorption and Excretion in Industry.
J. Occup. Med. Vol. 18, No. 10.

Reynolds, E.S., 1901.
An account of the epidemic outbreak of arsenical poisoning in beer drinkers in the north of England and Midland Counties in 1900.

Roth, F., 1957.
The sequellae of chronic arsenic poisoning in Moselle Vinters.
Germ. Med. Monthly 2: 172-175.

SAS 1979.
SAS User's Guide 1979 Edition.
SAS Institute Inc.
Cary, North Carolina.

Schroeder, H.A. and Balassa, J.J. 1966. Abnormal trace metals in man: arsenic. J. Chron. Dis. 19: 85-106.

Schroeder, H.A. and Mitchener, M., 1971.
Toxic Effects of Trace Elements on the Reproduction of Mice and Rats.
Arch. Env. Hlth. 23, 102-106.

Smith, D.C. Leduc, R. and Charbonneau, C. 1973.
Pesticide residues in the total diet in Canada.
III. 1971. Pestic. Sci. 4: 211-214.

Smith, T.J., Crecelius, E.A. and Reading, J.C.
Airborne Arsenic Exposure and Excretion of Methylated Arsenic Compounds.
Environ. Hlth. Prosp., 19, 89-93.

Snegiroff, L.S., and Lombard, O.L.M., 1951.
Arsenic and Cancer Observation in the Metallurgical Industry.
A.M.A. Arch. Ind. Hyg. 4: 199-205.

Sullivan, R.J. 1969. Air pollution aspects of arsenic and its compounds. Nat. Tech. Inform. Serv. Rep. PB 18807. 62pp.

Tseng, W.P., Chew, How, 1968.
Prevalence of Skin Cancer in an Endemic Area of Chronic Arsenicism in Taiwan:
J. Natl. Cancer Inst. 40, 453-63.

Underwood, E.J. 1971. Trace elements in human and animal nutrition. Academic Press, New York.
pp. 304-305, 357, 427-431.

U.S. Department of Health and Welfare, 1976.
Health Effects of Occupational Lead and Arsenic Exposure.
B.W. Carnow, Editor.

Vallee, B.L., Ulmer, D.D., and Wacker, W.E.C., 1960.
Arsenic Toxicity and Biochemistry.
A.M.A. Arch. Ind. Hlth. 21, 132-151.

Venugopal, B. and Luckey, T.D. 1978.
Metal Toxicity in Mammals-2- Chemical Toxicity of Metals and Metalloids. Plenum Press. New York and London.

Welch, K., Higgins, I. et al, 1982.
Arsenic Exposure, Smoking and Respiratory Cancer in Copper Smelter Workers.
Arch. Env. Hlth., Vol. 37, No. 6, pp. 325-335.

Whyte, A.V. 1983. Probability, Consequences and Values in the Perception of Risk in Proceedings of A Symposium on the Assessment of Risk and Perception of Risk to Human Health in Canada. October 18-19, 1982.

World Health Organization, 1973.
Trace Elements in Human Nutrition.
W.H.O. Tech. Rep. Ser. No. 532.

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